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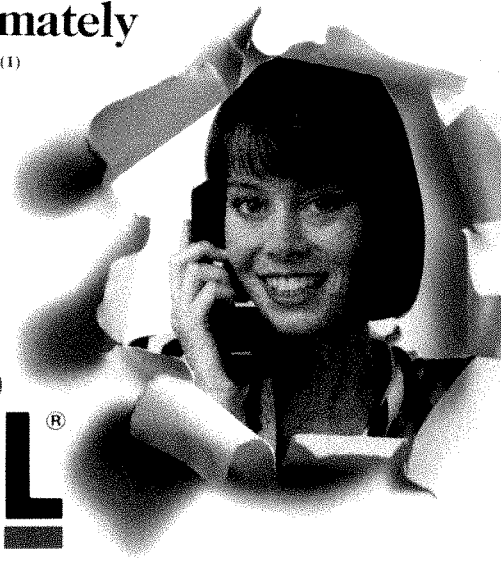
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HEREDITARY CEREBRAL HAEMORRHAGE WITH AMYLOIDOSIS—DUTCH TYPE

MAGNETIC RESONANCE IMAGING FINDINGS IN 7 CASES

by J. HAAN,¹ R. A. C. ROOS,¹ P. R. ALGRA,² J. B. K. LANSER,³
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SUMMARY

The clinical history and magnetic resonance imaging (MRI) findings are presented of 7 patients with hereditary cerebral haemorrhage with amyloidosis—Dutch type (HCHWA-D). The diagnosis was based on clinical and genealogical data, was confirmed in 3 patients at autopsy and in 2 others by biopsy. Focal neurological signs, and at least some degree of global cognitive deterioration, were observed in all patients, with unequivocal dementia in 4. MRI showed haemorrhages and areas of gliosis and, to a variable extent, hyperintensity of the white matter in T2-weighted images. Neuropathological examination revealed a large recent haemorrhage together with residual lesions from previous haemorrhages or infarcts in all patients examined. The white matter lesions, present on MRI, turned out to be areas of 'incomplete infarction' with demyelination. It is concluded that (hereditary) amyloid angiopathy can lead to strokes, but also to subcortical ischaemic encephalopathy. Amyloid angiopathy should therefore be considered in the differential diagnosis of white matter lesions, found on CT or MRI, especially when patients present with a cerebral haemorrhage. The relationship between HCHWA-D and Alzheimer's disease, another disease with cerebral amyloid deposition and diffuse white matter involvement, is discussed.

INTRODUCTION

Hereditary cerebral haemorrhage with amyloidosis—Dutch type (HCHWA-D) is a well-documented autosomal dominant disease, seen in 3 large families, (originally) resident in the Dutch coastal villages Katwijk and Scheveningen (Wattendorff *et al.*, 1982; Luyendijk *et al.*, 1988). In HCHWA-D, the first stroke usually occurs between the ages of 45 and 65 yrs, and is not caused by hypertension or haemorrhagic diathesis. Nausea, vomiting, progressive headache, focal neurological signs and impairment of consciousness are the most frequent signs and symptoms. Two-thirds of the patients die at the time of the first manifestation of their disease, whereas the remaining third will have two or more other strokes before death. The haemorrhages are equally distributed over both hemispheres, sparing the basal ganglia and the cerebellum. So far, the diagnosis has been confirmed by autopsy or brain biopsy in at least 60 patients (Luyendijk *et al.*, 1988). Extensive amyloid deposition in the cerebral arterioles and small leptomeningeal arteries has been found as the cause of the recurrent strokes.

The observation of diffuse white matter hyperintensity on magnetic resonance imaging

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(MRI) in a demented patient with HCHWA-D, who shortly before had had a cerebral haemorrhage (Case 2), induced us to carry out a systematic MRI study in patients with HCHWA-D. So far, 7 patients have been studied, and the findings obtained in them form the basis of this report.

METHODS

MRI was performed on a 0.5 Tesla Philips Gyroscan. In all cases transversal spin echo T1 (repetition time 600 ms, echo time 30 ms) and T2 (repetition time 3000 ms, echo time 60 ms) weighted images were obtained. Gadolinium-DTPA was administered intravenously in Cases 2 and 7. The extent and severity of periventricular white matter lesions (PWML) was determined in T2 images and expressed on a 0–4 scale (Brant-Zawadzki *et al.*, 1985). A PWML-score of zero indicates no lesions, a score of 1 denotes punctate foci of high signal intensity in the white matter immediately at the tip of the frontal horns of the lateral ventricles, a score of 2 indicates lesions elsewhere, but confined to the immediate subependymal region of the ventricles, a score of 3 denotes periventricular as well as separate, discrete, deep white matter foci of signal abnormality and a score of 4 indicates large and coalescent white matter foci.

All patients except Case 3 underwent neuropsychological examination, with repeat examination of Cases 2 and 5 after 2½ and 2 yrs, respectively. The following neuropsychological assessments were undertaken. (1) Intelligence quotient: the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981). (2) Mnestic functions: Wechsler Memory Scale form I (Wechsler, 1955). (3) Language: naming of 31 pictures of the Object-naming Test (Oldfield and Wingfield, 1965); verbal fluency by means of a controlled word association test using 4 letters (UNKA) with a time limit of 60 s (final score is the sum of the 4 subtotals) (Lezak, 1983); reading aloud a short story (scoring: number of dyslexic errors and rating on a 4-point scale: 0 = poor; 1 = fair; 2 = good; 3 = excellent) (Strub and Black, 1985); writing (own name, spontaneous sentences, 2 sentences to dictation, and reproduction of 2 sentences). The number of agraphic errors rated on the same 4-point scale (Strub and Black, 1985). (4) Constructional ability: reproduction of a cross, a star and cubes, and drawing trees on command, scored on a 4-point scale (Strub and Black, 1985). (5) Gnosis and praxis: disorders were determined by a screening examination (Strub and Black, 1985) and rated as good or impaired.

Biopsy samples were taken in Cases 2 and 5 during acute operative evacuation of a space-occupying haematoma, and autopsy was performed in 3 patients (Cases 1, 3, 4). Microscopic sections from coronal slices of brain were stained with haematoxylin-eosin, PAS, Klüver-Barrera, Congo red, thioflavin S and several silver stainings (Bielschowsky, von Braunmühl, Holmes, Palmgren and methenamine silver methods). For evaluation of the spatial distribution of the lesions, sections through both cerebral hemispheres were also studied in this way.

CASE REPORTS

Case 1 (Pedigree A, fig. 10)

This 47-yr-old woman was admitted because of headache, vomiting and word-finding problems in July 1986. She had never been seriously ill before but had had bilateral headaches for several months, occurring 2–3 times per week and each attack lasting approximately 3 h, without concomitant nausea or other symptoms. She was taking no medications. Her father had died at the age of 43 yrs as had one of her brothers at the age of 54, from cerebral haemorrhage. Another brother had had 2 cerebral haemorrhages at the age of 51.

On admission, her blood pressure was 120/80 mmHg. Neurological examination showed a right homonymous hemianopia, a mild right hemiparesis, alexia, and aphasia. A CT scan of the brain revealed a left temporoparietal haemorrhage. Angiography was normal, as were extensive laboratory investigations for clotting abnormalities or vasculitis. The patient improved moderately well and was discharged after 2 wks, only showing slight word-finding problems. Subsequently, her family noted slow deterioration of her memory. MRI was performed 2 wks after discharge and showed a region of high signal intensity in the left temporoparietal region in T1-weighted images, which was also of high signal intensity in T2-weighted

images, surrounded by a ring of low signal intensity (fig. 1). This finding indicated a primary cerebral haemorrhage or haemorrhagic infarct, with haemosiderin pigment.

Neuropsychological examination was performed in October 1986 and revealed a moderate impairment of intellectual and mnemonic functions, with word-finding, naming, reading, and writing disturbances, defective judgement of distance and geographic disorientation (Table 1). She was readmitted 6 months later, because of sudden impairment of consciousness. On admission she was comatose, had absent corneal reflexes, dilated unreactive pupils and irregular respiration. A CT brain scan now showed a large haemorrhage in the right temporal region and dilatation of the left lateral ventricle. She died 2 h after admission.

There were no abnormalities of the viscera at autopsy. The brain was oedematous (brain wt 1470 g). An old infarct was present in the border zone of white and grey matter of the left temporoparietal region. The right temporal region contained a recent haemorrhage, with dissection into the ventricles and the subarachnoid space. Microscopically, amyloid deposits were shown to be present in the small arteries of the leptomeninges, and the arterioles of cerebral and cerebellar cortex. The cerebral cortex contained many early senile plaques (without a demonstrable amyloid core) and occasionally a very small infarct. No neurofibrillary tangles were seen. The leptomeninges of this patient were used for biochemical characterization of the amyloid protein (Coria *et al.*, 1987; van Duinen *et al.*, 1987).

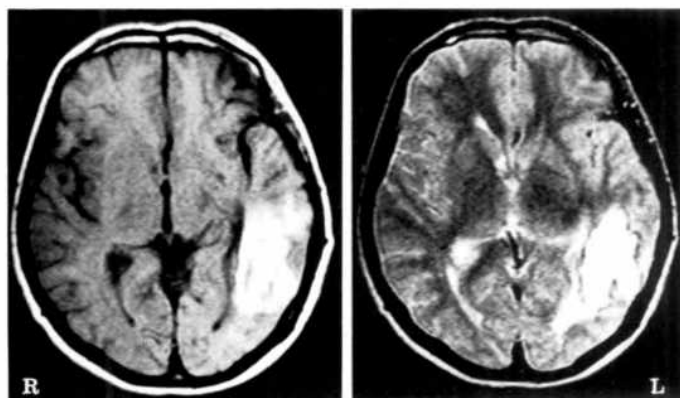


FIG. 1. MRI of Case 1. In T1-weighted images (left) a region of high signal intensity in the left temporoparietal region, extending into the angular gyrus is seen. In T2-weighted images (right), the same lesion again shows a high signal intensity and is surrounded by a ring of low signal intensity. Additional high intensity lesions are seen in the white matter of the left occipital lobe (PWML score 4).

Case 2 (Pedigree A, fig. 10)

This 45-yr-old woman was admitted because of headache, vomiting, and difficulty using her left arm in November 1979. She had never been seriously ill before and took no medications. Her grandmother, mother and one of her brothers had died from recurrent cerebral haemorrhages, at the ages of 48, 57 and 50 yrs, respectively.

On admission, her blood pressure was 120/90 mmHg. A left homonymous hemianopia and hemiparesis were present. Cerebral angiography and laboratory investigations were normal. A CT brain scan showed a haemorrhage in the right parietal region. Because of progressive impairment of consciousness the haemorrhage was evacuated. Amyloid deposits in all cortical arterioles as well as several cortical senile plaques of the primitive type (without amyloid core) were found in the cerebral biopsy. The patient recovered and was discharged after 6 wks with a left hemiparesis. She developed partial epilepsy, treated with carbamazepine. A repeat CT scan 1 yr later revealed calcification in the right parietal region.

The patient was readmitted in 1985 because of slowly progressive mental deterioration, amnesia, bradyphrenia, dyslexia and dysgraphia. Neurological examination showed an unchanged left hemianopia

and spastic hemiparesis. Furthermore, severe bradyphrenia, confusion, disorientation, memory impairment, aprosody, alexia, agraphia, acalculia, spatial disorientation were present. No metabolic cause for the mental impairment was found. A CT brain scan showed, in addition to the residual right hemisphere lesions, bilateral hypodense areas in the cerebral white matter. A neuropsychological examination, performed in October 1985, revealed severe impairment of intellectual and mnestic functions, with word-finding, reading and writing disturbances, constructional and ideomotor apraxia, and hemispatial neglect (Table 1). MRI was performed in November 1985 and showed a low signal lesion in the right parietal lobe and a punctate lesion of high signal in the left centrum semiovale on T1-weighted images. T2-weighted images showed mixed low and approximately isointensity in the right hemisphere lesion, surrounded by a ring of low signal intensity, suggesting that there had been several haemorrhages at the same site. The lesion in the left hemisphere still was of high signal intensity. Extensive high signal intensity was seen in the white matter of both hemispheres on T2-weighted images (fig. 2).

In August 1987, acute severe headache developed again. Two new haemorrhages were present on CT scan, 1 right parietal and 1 left occipital. The patient is currently living at home, but is fully dependent for all daily activities. A second neuropsychological examination in March 1989 documented a further deterioration of intellectual and mnestic functions (Table 1).

Case 3 (Pedigree A, fig. 10)

In March 1979, this 48-yr-old man suddenly experienced a heavy feeling in his right arm. Two days later, he had a generalized tonic-clonic seizure for which he was admitted. He was known to suffer from mild hypertension, but did not take medication.

On admission, his blood pressure was 180/100 mmHg. General examination was unremarkable. Expressive aphasia and a right hemiparesis were found. Laboratory investigation, a CT brain scan, cerebral angiography, lumbar CSF, cardiological status and Doppler ultrasonography of the carotid arteries all were normal. The hemiparesis improved slightly and the patient was discharged after 1 wk. In December 1979, he developed acute headache, followed by a tonic-clonic epileptic seizure. On admission, he was bradyphrenic, aphasic, and had a spastic right hemiparesis. A CT brain scan showed 2 hypodense lesions, 1 left occipital and 1 left parietal.

Two sisters, 2 uncles and 1 maternal aunt had died from autopsy-proven HCHWA-D; the mother probably also had died of intracerebral haemorrhage at the age of 60 yrs, but no autopsy was performed. The patient remained without symptoms, except for occasional epileptic seizures, for 4 yrs. A routine CT scan was

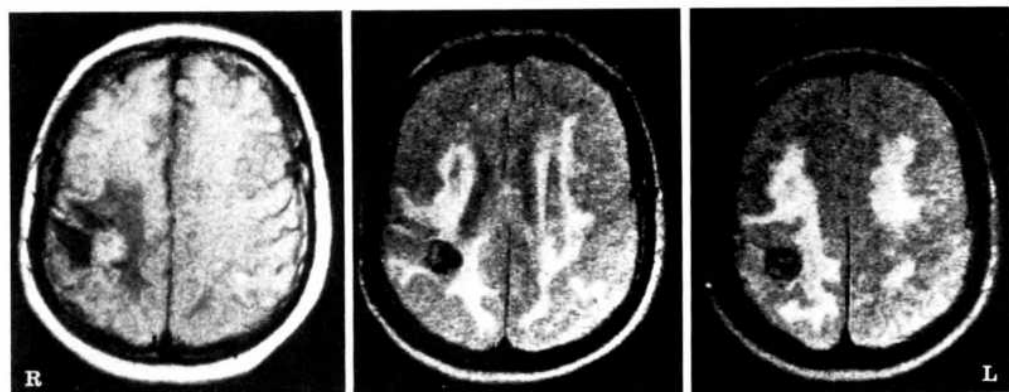


FIG. 2. MRI of Case 2. T1-weighted images (*left*) show a low signal lesion in the right parietal lobe, with a high signal component. A punctate lesion of high signal intensity is seen dorsally in the left centrum semiovale. In T2-weighted images (*middle and right*), the right parietal high signal component, which was seen on the T1-weighted images, is of mixed low and approximately isointensity, and surrounded by a ring-shaped structure of low signal intensity. The lesion, which was seen in the left centrum semiovale on T1-weighted images, is still of high signal intensity in T2-weighted images. Extensive high signal intensity is present in the white matter of both hemispheres, especially in the occipital lobes (PWML score 4). No additional lesions were detected on intravenous gadolinium-DTPA.

made, in April 1983 and, surprisingly, showed 2 small cerebral haemorrhages (1 in the left centrum semiovale, and 1 right occipital). Furthermore, generalized cerebral atrophy and hypodense lesions in the white matter were found.

In January 1986, the patient suddenly experienced clumsiness of the left arm and was readmitted. The history given by his wife revealed a decrease of memory and other mental functions over the preceding 3 yrs. Neurological examination now showed a spastic right hemiparesis and clumsiness of the left arm. He showed memory loss, bradyphrenia and disorientation. A new CT scan showed a haemorrhage in the right centrum semiovale. The patient was discharged 2 wks later. An MRI scan in September 1987 (fig. 3) on T1-weighted images showed low signal lesions in the left parietal and frontal regions, in the left centrum semiovale, in the right occipital region and in the right centrum semiovale, together with a high intensity lesion in the subcortical part of the right centrum semiovale. In T2-weighted images, all lesions seen on T1-weighted images were of high intensity, and the white matter of both hemispheres showed high signal intensity. These findings indicated several residual lesions from haemorrhages with gliosis, and a recent haemorrhage in the right centrum semiovale. In January 1989, he was admitted in a comatose state, with an acute left hemiplegia. A CT scan showed 2 new haemorrhages in the right hemisphere. The patient died within 2 days, at the age of 58, 10 yrs after his first symptom.

On neuropathological examination, the right cerebral hemisphere was oedematous and contained recent subcortical haemorrhages in the temporal (diameter 2 cm) and the parieto-occipital (diameter 4.5 cm) regions. In the left hemisphere, remnants of at least 3 old subcortical haemorrhagic infarcts (diameter of at least 5 cm each) were present. They were located in the frontal, parietal and occipital regions, respectively. These lesions were rather vaguely delimited from the adjacent white matter by areas of incomplete infarction, i.e., circumscribed areas in which, from focal hypoxic brain damage, the neuronal cell bodies, axons and myelin sheaths had disappeared, but glial cells and neuropil were preserved. In the white matter the 'U' fibres were fully preserved, but deep to them, demyelination was present. In the deepest areas this demyelination was accompanied by axonal depletion. The walls of the cortical arterioles and small leptomeningeal arteries contained amyloid deposits. Many early senile plaques (without an amyloid core) were observed in the cerebral cortex. No neurofibrillary tangles were found. Many very small infarcts were present in the cortex and white matter.

Case 4 (Pedigree A, fig. 10)

This 48-yr-old woman was admitted in November 1978 because of sudden headache, vomiting and impairment of consciousness. She had been complaining of paraesthesiae in the left arm followed by headache,

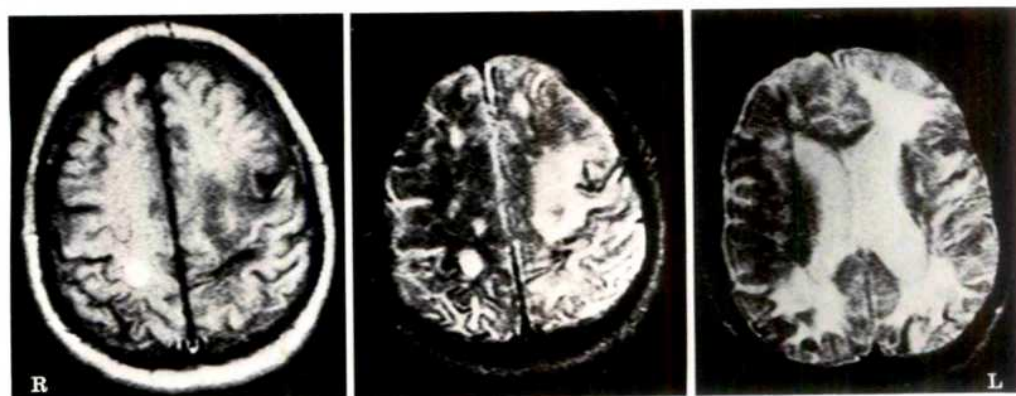


FIG. 3. MRI of Case 3. Generalized parenchymal loss is present in both hemispheres. In T1-weighted images (left) low signal regions are seen the left parietal and frontal regions, in the left centrum semiovale, the right occipital region and in the right centrum semiovale. A high intensity lesion is seen in the subcortical part of the right centrum semiovale. In T2-weighted images (middle and right) all lesions seen on T1-weighted images are of high intensity. The white matter of both hemispheres shows high signal intensity (PWML score 4).

lasting on each occasion for approximately 1 wk and with complete recovery in 1970 and 1974. She had never previously been ill, did not take any medications, and was not known to suffer from hypertension. Her father, 2 aunts and 2 uncles had died from cerebral haemorrhages at the ages of 56, 49, 55, 50 and 67 yrs, respectively.

On admission, she was stuporose, had a blood pressure of 110/90 mmHg and a left hemiparesis and homonymous hemianopia. Routine laboratory investigations were normal, as was cerebral angiography. A CT brain scan showed a large right temporoparietal haemorrhage. She recovered spontaneously and was discharged after 2 wks with a slight left hemiparesis, a homonymous hemianopia and constructional apraxia. Two yrs later she developed partial seizures, treated with phenytoin.

She developed acute headache followed by loss of consciousness after about 2 h in March 1982. On admission, a right hemiplegia and homonymous hemianopia were found. A CT scan showed a large left temporal haemorrhage and an old hypodense lesion at the site of the first haemorrhage in the right hemisphere. Two months later, on a follow-up CT scan, unexpectedly, a small right-sided haemorrhage was seen, in the region of the angular gyrus. She remained without complaints for 4 yrs. MRI was performed in June 1986 (fig. 4), and showed in T1-weighted images low intensity parenchymal defects in the right temporoparietal, occipital and left occipital regions. In T2-weighted images these lesions were of high signal intensity, and furthermore, high intensity lesions in white matter were seen. A neuropsychological examination in August 1986 revealed severe impairment of intellectual and mnemonic functions, with word-finding, naming, reading and writing disturbances, constructional apraxia and visual agnosia (Table 1).

She was readmitted in a comatose state in October 1986. A CT scan showed a new haemorrhage in the right hemisphere. She survived, severely disabled, but died from 2 new haemorrhages in April 1987, 9 yrs after the first cerebral haemorrhage. At autopsy, brain weight was 1350 g. In the right frontal region a large (2 × 8 cm) recent cortical haemorrhagic infarct extending into the white matter was found, as well as incomplete infarction, with demyelination and incomplete demarcation in the left frontal region (fig. 5). The histological features of this incomplete infarction were the same as described in Case 3. Large numbers of cortical arterioles and leptomeningeal small arteries showed infiltration with amyloid, and many early plaques (without amyloid cores) were present in the cerebral cortex. No neurofibrillary tangles were found. Many microinfarcts were observed.

Case 5 (Pedigree B, fig. 11)

This 45-yr-old man was admitted because of headache, nausea and vomiting of sudden onset in May 1973. He had never been seriously ill before and was not known to suffer from hypertension. His father, 5 brothers and 1 sister had died from autopsy-proven HCHWA-D. His blood pressure was 140/90 mmHg.

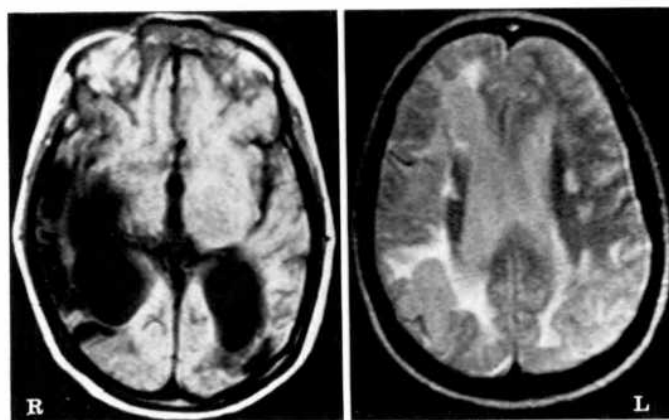


FIG. 4. MRI of Case 4. In T1-weighted images (*left*) a dilated ventricular system and parenchymal loss in both hemispheres are seen. Low intensity parenchymal defects are seen in the right temporoparietal, occipital and left occipital regions. In T2-weighted images (*right*) high intensity lesions in the white matter are seen (PWML score 3).

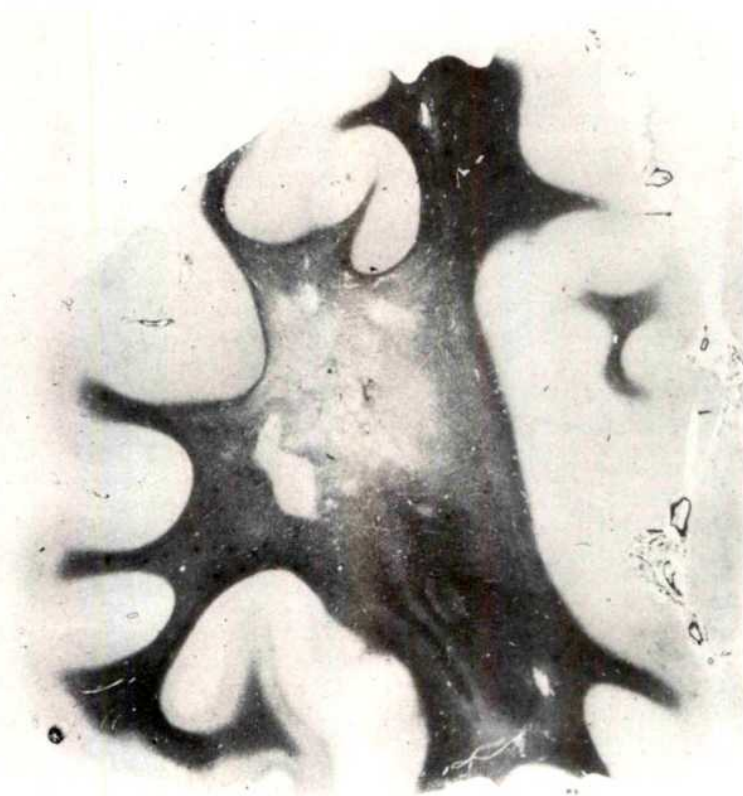


FIG. 5. Section through left frontal lobe in *Case 4*. The white matter shows an area of demyelination accompanied by a depletion of axons (myelin stain; Klüver-Barrera; $\times 1.5$).

General examination was unremarkable. He was drowsy and there was nuchal rigidity. Pneumoencephalography and cerebral angiography suggested a right temporal mass lesion. Two days after admission, he developed a left hemiparesis and became comatose. A large right temporal haematoma was removed. In the biopsy specimen, some leptomeningeal arterioles were infiltrated with amyloid. The biopsy contained no brain parenchyma. The patient recovered and was discharged with a left supranuclear facial paresis. He was readmitted in 1975 because of severe headache. No neurological abnormalities were present but lumbar puncture revealed haemorrhagic CSF.

In July 1979, a new episode of headache led to readmission. He then showed severe bradyphrenia, neck stiffness and a left hemiparesis. The first CT scan revealed a right temporal haemorrhage with leakage into the right ventricle, and 2 hypodense areas in the left frontal and right parietal lobes. The patient recovered spontaneously but developed tonic-clonic seizures.

In 1986, his family reported progressive apathy, memory loss and gradual impairment of reading and writing, which had begun in about 1984. On CT scan multiple residual lesions of previous strokes were seen, and white matter hypodensity. MRI was performed in July 1986 (fig. 6), and showed in T1-weighted images hypointense lesions in the right parietal and occipital lobes and the left frontal lobe. These lesions were of slightly increased intensity in T2-weighted images and some of them were surrounded by a rim of low signal intensity. A neuropsychological examination in August 1986 (Table 1) revealed moderate impairment of intellectual and mnemonic functions, with mild word-finding problems and mild constructional apraxia.

Although no new strokes occurred after 1986, the patient gradually became confused, aggressive and demented. Extensive laboratory investigation failed to detect any abnormalities. A second neuropsychological examination was performed in December 1988 (Table 1). This revealed severe impairment of intellectual and mnemonic functions, with increased word-finding and naming problems, perseveration, spatial disorientation and severe constructional apraxia (fig. 7). The patient lived at home until recently, but his behavioural disturbances have now made admission to a psychiatric hospital necessary.

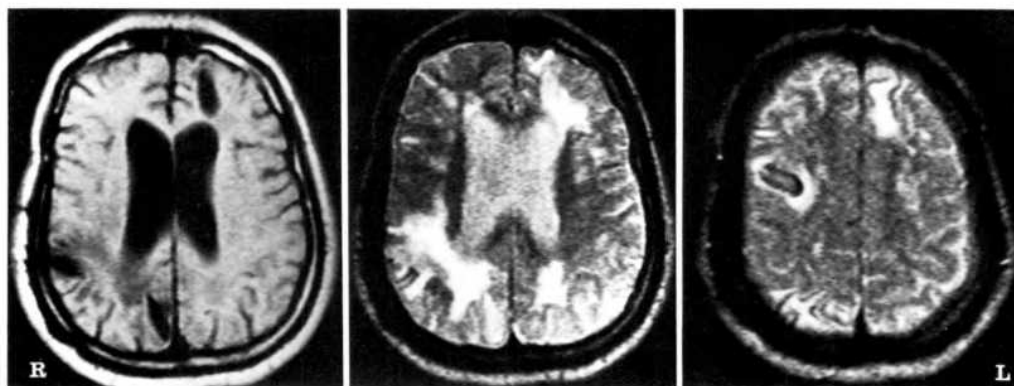


FIG. 6. MRI of Case 5. T1-weighted images (*left*) show lesions with reduced signal in the right parietal and occipital lobes and the left frontal lobe. These lesions are of slightly increased intensity in T2-weighted images (*middle*). On a higher section of the T2-weighted images (*right*), a nearly isointense lesion, high in the right parietal lobe, is surrounded by a rim of low signal intensity. White matter high intensity lesions are present (PWML score 4).

Case 6 (Pedigree A, fig. 10)

This man suffered from headache attacks since the age of 35 yrs, each time lasting approximately 3 h and occurring twice a week, without nausea, vomiting or other symptoms. In May 1985, at the age of 45 he attended the outpatient department because of a single severe episode of headache that lasted longer and was accompanied by a heavy feeling in the right arm which disappeared after 1 h. His father had died from cerebral infarction at the age of 63 yrs, and 2 aunts and 4 uncles had suffered from cerebral

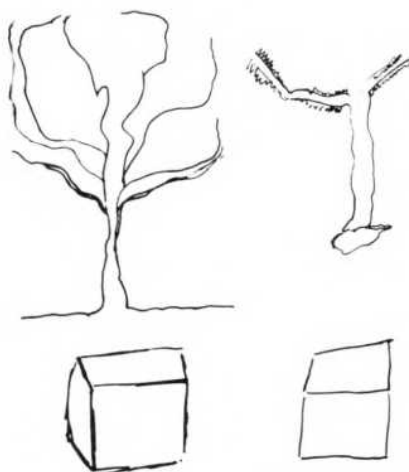


FIG. 7. Examples of the neuropsychological performance of Case 5 on 2 occasions. *Left*, drawing to command of a tree (*top*) and reproduction of a cube (*bottom*) during the examination in August 1986, showing mild constructional apraxia. *Right*, drawings after the same commands in December 1988, showing more severe constructional apraxia.

haemorrhages. In 1 aunt, the diagnosis HCHWA-D was made at autopsy. Neurological examination and CT scan were unremarkable.

In July and November 1986, he suffered from 2 more attacks of headache with a strange feeling in the right arm, but each time neurological examination was normal. In October 1987, another severe headache led to admission to hospital. His blood pressure was 130/80. The patient had a right hemiparesis with an extensor plantar response. A CT brain scan revealed 1 hyperdense lesion in the left frontal and 1 in the left occipital region. Cerebral angiography was normal, as was cardiological investigation. Clear colourless CSF with a pleocytosis of 51 white cells/ μ l was obtained by lumbar puncture.

The patient improved and was discharged without neurological abnormalities. MRI was performed in July 1988 (fig. 8), and showed no abnormalities in T1-weighted images, whereas T2-weighted images showed several periventricular punctate lesions and discrete foci in the deep hemisphere white matter with high signal intensity.

In December 1988, a further CT scan showed that the 2 hyperdense lesions detected on CT scan in 1987 had evolved into hypodense areas. The patient still suffered from attacks of headache, sometimes accompanied by a transient right hemiparesis. Neuropsychological examination, performed in February 1989 (Table 1), only revealed slight constructional apraxia.

Case 7 (Pedigree B, fig. 11)

This 46-yr-old woman had suffered from transient headaches since her youth. She had severe frontal headache, disappearing spontaneously after several hours, in September 1987. Biopsy material from a carpal tunnel decompression operation in 1988 was normal. One week after the operation, the patient's sister, aged 45 yrs, suddenly died because of a large cerebral haemorrhagic infarction. At autopsy, cerebral amyloid angiopathy was found. The family history revealed that her father and 4 of his brothers and sisters all had died of recurrent cerebral haemorrhages. For this reason, a CT scan in our patient was performed and revealed hypodense lesions in the left occipital and right frontal regions. Cerebral angiography was normal as was extensive laboratory study of blood coagulation.

Neuropsychological investigation was performed in November 1988 (Table 1) and revealed mild constructional apraxia. MRI was obtained in December 1988 (fig. 9), and showed in T1-weighted images areas with low signal intensity in the right frontal and left parietal lobes. T2-weighted images showed high signal emission from the right frontal lesion. Low signal adjacent to a high intensity lesion suggested a haemorrhagic origin of the left parietal lesion.

The patient is now living at home without complaints or symptoms. In her 40-yr-old asymptomatic younger sister (7A in pedigree B, fig. 11) MRI was performed which was unremarkable.

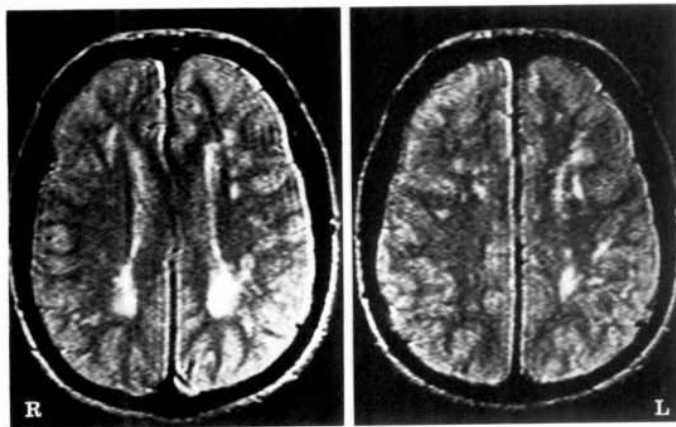


FIG. 8. MRI of Case 6. T1-weighted images were normal. T2-weighted images (*left and right*) show several punctate periventricular lesions and discrete foci in the deep white matter of the hemispheres with high signal intensity (PWML score 2).

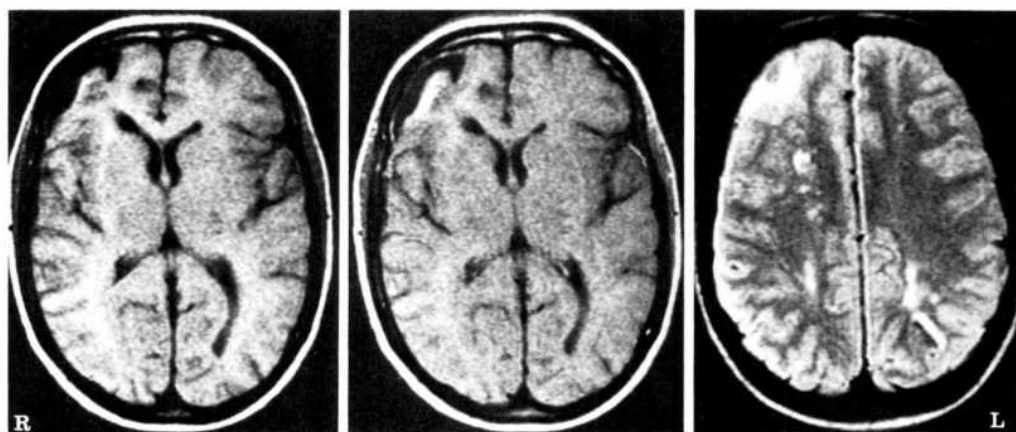


FIG. 9. MRI of Case 7. In T1-weighted images (*left*) an area with low signal intensity is seen in the right frontal lobe. After intravenously administered gadolinium-DTPA (*middle*), enhancement is seen in this lesion. A higher section of the T2-weighted images (*right*) shows a high signal lesion in the right frontal lobe, and low signal adjacent to a high intensity lesion in the left parietal region. Multiple periventricular lesions of high signal are seen (PWML score 2).

SUMMARY OF RESULTS

Genealogical trees (Pedigrees A and B, figs 10, 11)

The following genetic characters can be established from the pedigrees. (1) The disease has appeared in several generations without interruption. (2) The disease attacks both sexes. (3) The disease has been transmitted from female to male, from female to female, and from male to male. The family tree corresponds to what is to be expected with autosomal dominant transmission (Luyendijk *et al.*, 1988).

Neuropsychological examination

In all patients at least some disturbance of cognitive functions was found (Table 1). Mild to severe impairment of intellectual and mnemonic functions was present with specific disturbances of construction, language, praxis and gnosis. The 2 patients who were examined twice showed progressive mental deterioration. Case 5 had had no clinical signs of stroke between the 2 neuropsychological examinations.

Magnetic resonance imaging

MRI examination revealed many focal lesions. Some of these showed high signal emission in T1 as well as T2-weighted images, suggesting recent haemorrhages. Others were of low signal intensity in T1 and of high signal intensity in T2-weighted images, often surrounded by an area of very low signal emission, indicating gliosis in residual lesions from previous haemorrhages with a haemosiderin rim. No cerebellar or brainstem lesions were visible. In all patients, high intensity lesions of subcortical white matter were visible on T2-weighted images.

Neuropathological examination

Sclerotic changes with amyloid deposits in a large proportion of the cortical arterioles and the small leptomeningeal arteries and arterioles were present. Furthermore, large recent and old lobular haemorrhages and haemorrhagic infarcts of the white matter, and many small haemorrhagic infarcts of the cortex and subcortical white matter, were found. Finally, large areas of demyelination were observed in deep white matter, with loss also of axons. There were many early plaques (without amyloid cores) in the cerebral cortex. No neurofibrillary tangles were observed in any of the cases.

TABLE 1 NEUROPSYCHOLOGICAL FINDINGS

Cases	1	2	4	5	6	7
Date of test	Oct. 1986	Oct. 1985	Mar. 1988	Aug. 1986	Aug. 1986	Nov 1988
WAIS (R)						
Verbal IQ	79	68	60	66	81	93
Performance IQ	74	<50	<50	NP	77	100
Full scale IQ	74	55	50		79	95
Wechsler Memory Scale	90	60	53	62	76	103
Language						
Naming	12	15	8	6	26	28
Verbal fluency	20	11	10	5	19	26
Reading	0	0	0	0	2	3
Writing	0	0	0	0	2	1
Construction						
Reproduction of drawings	1	0	0	0	2	1
Drawings to command	1	0	0	0	1	3
Praxis						
Ideomotor praxis	G	I	G	G	G	G
Ideational praxis	G	NP	NP	NP	G	G
Right-left orientation	G	NP	I	G	G	G
Gnosis						
Finger gnosis	G	NP	I	G	G	G
Visual gnosis	G	I	I	I	G	G
Stereognosis	G	NP	I	G	G	G
Geographic orientation	I	NP	I	NP	G	G

WAIS (R) = Wechsler Adult Intelligence Scale (revised), IQ = Intelligence Quotient; WF = word-finding problems, P = perseverations; G = good; I = impaired; NP = not performed

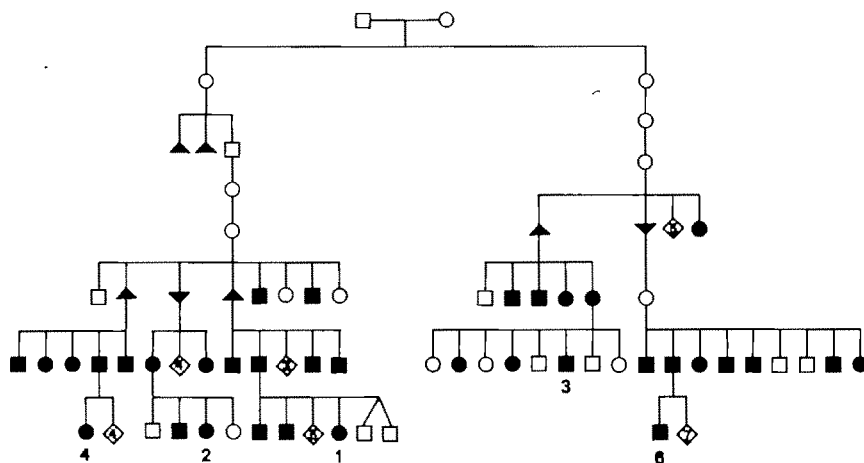


FIG. 10. Pedigree A. The numbers 1, 2, 3, 4, 6 correspond to the respective case reports. Pathologically or radiologically-proven cerebral haemorrhage (■ ●). No haemorrhage or insufficient information (□ ○). Cerebral haemorrhage by history (▲ ▼). Number of unaffected offspring (◆)

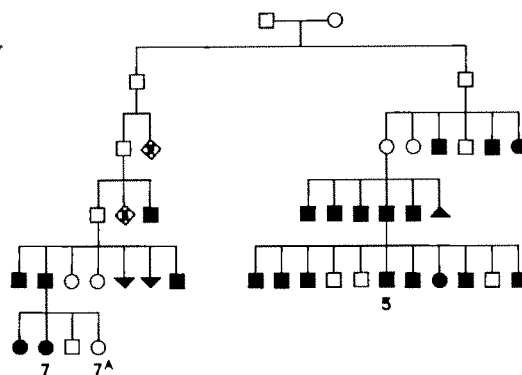


FIG. 11. Pedigree B. The numbers 5, 7, 7^A correspond to the respective case reports. Symbols as for fig. 10.

DISCUSSION

These case presentations are fairly stereotyped examples of the clinical course of HCHWA-D: a stroke as the first manifestation, sometimes preceded for variable periods by migraine-like headaches, and followed by recurrent cerebral haemorrhages, leading to severe disability, dementia and death within some years. The focal neurological and neuropsychological symptoms are traditionally attributed to the strokes, but not all haemorrhages cause symptoms: in some of the patients clinically unsuspected haemorrhages were detected on routine CT scans. Progressive mental deterioration was documented in 2 patients (Cases 2, 5) by 2 separate neuropsychological examinations, and in the other patients at least some degree of cognitive deterioration was documented

by a single neuropsychological examination (Table 1). This deterioration could have been caused by multiple small infarcts as detected on neuropathological examination or by 'clinically silent' haemorrhages, as mentioned above.

CT and MRI examination showed several haemorrhages and residual lesions from previous strokes in all patients. The MRI, in particular, reflected the complicated time spectrum of haemorrhages, dependent on the breakdown products of blood (Bradley, 1987). On MRI of Cases 1 and 3, areas of high signal emission were seen in T1 as well as in T2 images, suggesting primary cerebral haemorrhages or haemorrhagic infarction. Neither CT nor MRI can distinguish with certainty between these two types of stroke (Hecht-Leavitt *et al.*, 1986). In the other 5 cases, T1-weighted images showed areas of low signal emission, with high signal emission in T2-weighted images. These findings are compatible with gliosis in residual lesions from previous strokes (Bradley, 1987). The enhancement after intravenous gadolinium-DTPA in Case 7 was probably due to increased permeability of the blood-brain barrier after a recent haemorrhagic infarct. In Cases 1, 2 and 5 an area of very low signal emission around the cortical lesions indicated the presence of haemosiderin pigment. This phenomenon is frequently seen in, but is not pathognomonic for, primary cerebral haemorrhage (Hecht-Leavitt *et al.*, 1986; Barkovich and Atlas, 1988).

Three cases showed periventricular white matter lesions (PWML) on CT scan (Cases 2, 3, 5), whereas the T2-weighted MRI scans showed PWML in all cases. This confirms the superiority of MRI as compared with CT in detecting abnormalities of the subcortical white matter (Johnson *et al.*, 1987). In one of the previous reports of cerebral amyloidosis studied by MRI (published in abstract form, without illustrations), PWML were also found on T2-weighted images in 3 of 4 patients investigated (Loes *et al.*, 1988).

PWML appear to reflect nonspecific, mostly vascular, damage to the brain (Awad *et al.*, 1986; Gupta *et al.*, 1988; Scheinberg, 1988). CT or MRI procedures showed PWML in 14 of 48 patients with pathologically proven cerebrovascular amyloidosis (Table 2). This finding indicates that cerebrovascular amyloid angiopathy (hereditary or sporadic) has to be included in the differential diagnosis of PWML seen on CT or MRI. Neuropathological investigation of PWML, as visible on CT or MRI, in sporadic cases of autopsy or biopsy proven amyloid angiopathy (Table 2), has revealed demyelination (Bogucki *et al.*, 1988), myelin loss with U fibre sparing and incomplete infarction (Gray *et al.*, 1985), and 'myelin pallor' without demyelination or infarction (Rezek *et al.*, 1987). Stenosis in the meningocortical segments of the long perforating arterioles by amyloid deposits with consequent chronic hypoperfusion of the deep white matter seems to be the probable pathogenetic mechanism for PWML (Gray *et al.*, 1985). The contribution of this hypoperfusion can be studied in HCHWA-D, as there is extensive amyloid deposition in cortical arterioles. Pathological examination of the patients described here showed amyloid deposits in a large proportion of the cortical arterioles and meningeal small arteries and arterioles. Haemorrhages or haemorrhagic infarcts were found in all patients. The cerebral cortex and adjacent subcortical white matter often contained scattered small infarcts. In all cases, PWML were present on MRI and in Cases 3 and 4 these lesions were studied neuropathologically. In both of them a lesion was present of the white matter, with marked demyelination and central rarefaction of axons, and with features of so-called 'incomplete infarction', a circumscribed area in which the neuronal cell bodies, axons and myelin sheaths have disappeared, but glial

cells and neuropil are preserved. These lesions could not be explained by the presence of cortical infarcts, leading to adjacent subcortical hypoperfusion, as they were also found in absence of cortical infarcts (fig. 5). Clearly, cortical and leptomeningeal vascular amyloid angiopathy leads to a subcortical ischaemic encephalopathy, which is, to some extent at least, visible on CT and MRI.

It has recently been shown that the vascular amyloid in HCHWA-D is homologous with the β -protein found in brains of patients with Alzheimer's disease (AD) (Coria *et al.*, 1987; van Duinen *et al.*, 1987). Cerebrovascular amyloid is present in most patients with AD (Joachim *et al.*, 1988) and has been implicated in the pathogenesis of AD by some authors (Glennner *et al.*, 1981). In this 'vascular' theory, primary amyloid deposition occurs in the walls of the cerebral blood vessels, and other amyloid deposits (senile plaques and neurofibrillary tangles) develop secondarily (Glennner *et al.*, 1981). Comparison of the clinical and neuropsychological features of our patients with HCHWA-D with those reported in patients with AD is difficult as many of the cognitive deficits in patients with HCHWA-D presumably result from vascular lesions. The dementia patterns of AD and multi-infarct dementia cannot be separated qualitatively (Scheinberg, 1988). The neuropsychological characteristics of AD, namely amnesia, language disorders and perceptuospatial deficits were present at least to some degree in our patients, but their presence could be explained by focal cortical lesions. Other neuropsychological disturbances were also found (Table 1).

Radiological examination of patients with HCHWA-D revealed many focal lesions and also PWML. In the investigation of dementia, PWML on CT and MRI have been found in patients with multi-infarct dementia (Erkinjuntti *et al.*, 1987; Harrell *et al.*, 1987; Hershey *et al.*, 1987), as well as in patients with AD (Erkinjuntti *et al.*, 1987; Harrell *et al.*, 1987). The presence of these lesions therefore does not discriminate

TABLE 2. RADIOLOGICAL INVESTIGATIONS IN 48 PATIENTS WITH PATHOLOGICALLY PROVEN CEREBRAL AMYLOID ANGIOPATHY

Reference	No. of patients	Method	Result
Tyler <i>et al.</i> , 1982	1	CT	Haemorrhages
Juhon <i>et al.</i> , 1983	1	CT	Haemorrhages
Gilbert and Vinters, 1983	4	CT	Haemorrhages
Kalyan-Raman and Kalyan-Raman, 1984	10	CT	Haemorrhages
Gilles <i>et al.</i> , 1984	4	CT	Haemorrhages
Gray <i>et al.</i> , 1985	4	CT	Normal 1, PWML 3
Cosgrove <i>et al.</i> , 1985	11	CT	Haemorrhages
Nadeau <i>et al.</i> , 1987	1	CT	PWML
Rzezak <i>et al.</i> , 1987	1	CT	PWML
Bogucki <i>et al.</i> , 1988	1	CT	PWML
Drayer, 1988	1	MRI	Haemorrhages
Loes <i>et al.</i> , 1988	4	MRI	PWML 3, Haemorrhages 2
This report	5	MRI	PWML 5, Haemorrhages 5
Totals	48	CT 38 MRI 10	Haemorrhages 39 PWML 14 Normal 1

PWML = periventricular white matter lesions.

between multi-infarct dementia and AD. Consequently, the finding of PWML in patients with HCHWA-D also cannot be used as an argument in favour of any relation between HCHWA-D and AD.

Neuropathological examination revealed early plaques without any amyloid core (Wisniewski *et al.*, 1989) in Cases 1, 2, 3 and 4. Neurofibrillary tangles were absent. This finding has been reported before in HCHWA-D and it was concluded that in HCHWA-D, the neuronal population is not involved in amyloidogenesis (van Duinen *et al.*, 1987; Castaño and Frangione, 1988). However, it might be possible that patients with HCHWA-D die before typical senile plaques or neurofibrillary tangles develop.

Another neuropathological finding was the areas of 'incomplete infarction' with demyelination in Cases 3 and 4. These lesions resemble the 'selective incomplete white matter infarctions' found in patients with AD, which appear not to be caused by subcortical amyloid angiopathy (Englund *et al.*, 1988). A possible relation with hypoperfusion by cortical amyloid angiopathy, the possible mechanism in HCHWA-D, has not so far been investigated.

Too many differences between HCHWA-D and AD exist to conclude that HCHWA-D is 'Familial AD, vascular type'. HCHWA-D and probably also sporadic cerebral amyloid angiopathy have to be included in the differential diagnosis of dementia. Some of the clinical, radiological and neuropathological results we found in patients with HCHWA-D could have implications for further research in HCHWA-D as well as for AD.

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A STUDY OF IMMUNOGLOBULIN G IN THE CEREBROSPINAL FLUID OF 1007 PATIENTS WITH SUSPECTED NEUROLOGICAL DISEASE USING ISOELECTRIC FOCUSING AND THE LOG IgG-INDEX

A COMPARISON AND DIAGNOSTIC APPLICATIONS

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SUMMARY

Cerebrospinal fluid and serum immunoglobulin G from 1007 patients with suspected neurological disease were analysed by 2 methods: isoelectric focusing for the detection of oligoclonal banding, and quantitative measurement of IgG and albumin for the formulation of a Log IgG-Index. A comparison of the 2 methods in the detection of local synthesis of IgG showed that isoelectric focusing not only gave a much higher yield overall, with 282 patients showing local synthesis versus 225 for the Log IgG-Index, but also a higher specificity, with a false positive rate of 0% versus 3.5%. In addition, of the 282 patients positive by isoelectric focusing only 163 (58%) were positive by the Log IgG-Index.

Of the 1007 patients studied, 206 had multiple sclerosis (MS), and isoelectric focusing showed local synthesis in 95% of clinically definite cases, with a 90% detection rate overall. The Log IgG-Index was positive in only 67% of clinically definite cases, with an overall 59% detection rate. Thus with the exceptions noted above, local synthesis of IgG as defined by isoelectric focusing is confined to demyelinating, inflammatory, infectious and postinfectious disorders.

Our results compare very favourably with the published sensitivities of magnetic resonance imaging in the detection of abnormalities in multiple sclerosis, and better than those for evoked potentials. Where both these investigations are readily available isoelectric focusing provides a useful adjunct. For the majority of physicians and neurologists who do not have ready access to magnetic resonance imaging, isoelectric focusing is an excellent alternative. We would also recommend that it become the standard for the measurement of IgG abnormalities in the cerebrospinal fluid and that the use of quantitative data be abandoned for routine purposes.

INTRODUCTION

There are few laboratory tests routinely available to the clinician that aid in the diagnosis of disorders of the nervous system. Many investigations commonplace in major centres, such as magnetic resonance imaging (MRI) and sophisticated electrophysiology are not available to the majority of neurological departments in the UK and elsewhere. We have long been aware of immunological abnormalities in neurological disease, and the study of the immunoglobulin fractions in cerebrospinal fluid (CSF) has become well established as part of the laboratory support for the diagnosis of a number of disorders, most notably

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multiple sclerosis (MS) (Kabat *et al.*, 1942, 1948; Delmotte and Gonsette, 1977; Sidén and Kjellin, 1978).

Immunoglobulins can be measured quantitatively, and the results expressed using a variety of formulae to indicate the presence of intrathecally synthesized antibody (Yahr *et al.*, 1954; Link and Müller, 1971; Tourtellotte, 1975; Link and Tibbling, 1977; Tibbling *et al.*, 1977; Schuller and Sagar, 1981; Reiber and Felgenhauer, 1987). From the 1960s, qualitative abnormalities in the CSF immunoglobulins, specifically IgG, became apparent. These took the form of IgG of restricted heterogeneity, and became known as oligoclonal banding (OCB) (Lowenthal *et al.*, 1960; Laterre *et al.*, 1970; Link, 1973; Vandvik and Skrede, 1973). With the advent of sophisticated neuroradiology and electrophysiology, and the choice of laboratory techniques now available to study CSF IgG, we have sought to establish the best method of detection of these IgG abnormalities, the spectrum of neurological disease in which such abnormalities may be found, their usefulness as a discriminator between categories of neurological disease, and how useful a predictor of disease they may be. We have especially considered the role of laboratory tests in the diagnosis of MS, which still presents formidable diagnostic problems for the clinician.

MATERIAL AND METHODS

The study was a retrospective analysis, with the same investigator interpreting the laboratory results and examining the clinical notes for all patients in the study.

Patients

Over a 2½ year period, 1137 inpatients at the National Hospitals for Nervous Diseases had paired sera and CSF analysed as part of routine laboratory investigations. All samples were analysed and the isoelectric focusing (IEF) interpreted without reference to clinical details, which were usually not available at the time of analysis, and further protected by the use of sample coding. Of this number, 1007 patients had notes giving full clinical details which could be inspected personally.

Disease classification

The classification used was an in-house method based upon the International Classification (World Health Organization, 1977), and patients were grouped further into 18 broad pathological headings. For MS patients, the clinical classification of McDonald and Halliday (1977) was applied. The patients were categorized using information available at the time of admission for the lumbar puncture.

Isoelectric focusing

IEF was performed on a 22.6×11.5 cm agarose plate (Walker *et al.*, 1983). This was made by taking 3.6 g sorbitol (Sigma, Poole, UK), 3.6 g agarose (IEF grade, Pharmacia, Milton Keynes, UK) in 30 ml 10% glycerol, and heating in a boiling water bath until dissolved. When the mixture had cooled to 60° C, 2 ml pH 3.0–10.0 and 0.5 ml pH 8.0–10.5 ampholyte (Pharmacia) was added, and then well mixed (being careful not to introduce any air bubbles). Using a sample application foil (Pharmacia, Milton Keynes, UK), approximately 100 ng of IgG was applied to the gel surface, giving a typical loading volume of between 2 and 15 µl CSF. The samples were run for 1½ h at 1250 V on a Pharmacia IEF 3000 system (maximum voltage, current, and power were set at 1250 V, 150 mA, and 18 W, respectively, per plate). When the run was complete the separated sample was transferred passively to a nitrocellulose membrane (Sartorius, Belmont, UK) by squashing the gel for 30 min. IgG was stained immunochemically by first blocking the membrane with 2% skimmed milk in saline (30 min), incubating with goat antihuman Fc-specific IgG (Atlantic Antibodies, Winnersh, UK; diluted 1/1000 in 50 ml 0.2% milk solution for 30 min), finally incubating with horseradish peroxidase labelled rabbit anti-goat immunoglobulins (DAKO, High

Wycombe, UK, diluted 1/1000 in 50 ml 0.2% milk solution for 30 min), with adequate washing with 0.2% milk solution in saline between steps. The colour was developed, after washing with water, by incubating the membrane in 50 ml colour reagent (30 mg 3-amino-9-ethylcarbazole (Sigma, Poole, UK), dissolved in 10 ml methanol and the volume made to 50 ml with 0.02 M acetate buffer, pH 5.2). After 10 to 15 min the membrane was washed in water and dried using hot air. CSF samples were initially run, and if positive for oligoclonal bands then 5 μ l diluted serum (1/500 in distilled water) was run with the CSF in adjacent lanes.

IgG and albumin measurements

IgG and albumin concentrations in CSF and serum were determined using a 'monorocket' technique (Laurell, 1972). For IgG a 1.5 mm thick gel was used (1% HEE0 agarose, 0.5% ME agarose (SeaKem, Rockland, Maine, USA), and 15% PEG 6000 in 0.075 M barbitone buffer pH 8.6) and for albumin a 1 mm thick gel (1% ME agarose, and 3% PEG 6000 in 0.075 M barbitone buffer pH 8.6). The volume of anti-IgG and antialbumin (Atlantic Antibodies, Wincoburn, UK) used was adjusted for each batch of antisera to give a peak of approximately 30 mm for a concentration of 200 mg/l IgG or 500 mg/l albumin. The volume used varied between 80 and 120 μ l depending on the batch of antisera. Serum samples were diluted 1/200 in saline and ran in adjacent wells to their corresponding CSF samples. 2 μ l and 4 μ l of sample were used for albumin and IgG, respectively. The plates were run overnight at 80–100 mA with 0.075 M barbitone buffer, pH 8.6 as the electrode buffer. The peaks were stained using Coomassie brilliant blue G-250 (BDH, Dagenham, UK, C.I. 42655) after twice washing the gel in saline, squashing dry between washes and before staining. Results were calculated using a second-order curve-fit programme, comparing test peak heights with standards of known composition.

Total protein measurement

The total protein was measured by turbidimetry using benzethonium chloride (Luxton *et al.*, 1989). Briefly, 10 μ l of unconcentrated CSF was mixed with 190 μ l benzethonium chloride reagent (5 g/l benzethonium chloride, 20 g/l EDTA, 20 g/l NaOH) in a microtitre plate well. After standing for 10 min the optical density at 410 nm was read by a Dynatech automated plate reader.

Interpretation of results

IEF was interpreted by a single investigator. Local synthesis was defined as the presence of 3 or more bands in the CSF not matched in serum. CSF and serum pairs were classified into 5 groupings: (1) local synthesis with no serum bands (+); (2) local synthesis plus serum bands (>); (3) leakage of serum bands into CSF, i.e., identical pattern in serum and CSF (*); (4) paraprotein (P); (5) no bands (–).

Establishing the optimum quantitative formula

Six different quantitative formulae were applied to the IgG and albumin values obtained on the 1007 patients in order to establish the optimum method for comparison with IEF. The full technical analysis is being published elsewhere (Luxton *et al.*, 1990). The 6 formulae used were: (1) IgG Index (Tibbling *et al.*, 1977); (2) IgG/albumin ratio (Tibbling *et al.*, 1977); (3) Schuller formula (Schuller and Sagar, 1981); (4) Tourtellotte formula (Tourtellotte, 1975); (5) Reiber formula (Reiber and Felgenhauer, 1987); (6) Log IgG-Index (Thompson, 1988).

The Log IgG-Index was calculated from the following formula:

$$\text{Ln} [(IgG_c/IgG_s)/(Alb_c/Alb_s)] + 1$$

where c = cerebrospinal fluid, s = serum, Alb = albumin. For each formula, the sensitivity, specificity and efficiency were calculated at a range of cut-off values in order to establish an optimum upper limit of normal for each formula on the basis of its maximum efficiency at assessing local synthesis when compared to IEF. The formulae were then compared in terms of their overall efficiency curves. The formulae giving the best efficiency curves were the IgG Index and the Log IgG-Index, followed by, in decreasing order, the Reiber, Tourtellotte, IgG/albumin ratio and Schuller formulae. Further analysis of residuals of the two best formulae showed that the Log IgG-Index gave a much more even scatter around the line of best fit, and thus overall was the best formula. The optimum cut-off value for the Log IgG-Index was established from the efficiency curve at 0.84. All values above this are taken as evidence of local synthesis of IgG.

RESULTS

Of the 1007 patients, 282 had local synthesis of IgG by IEF criteria, and 725 had no local synthesis (Table 1). By quantitative analysis, 225 had local synthesis and 782 had no local synthesis. There was agreement between the 2 methods on only 163 patients for local synthesis, and 663 for absence of local synthesis, leaving 181 patients for which there was a discrepancy. This latter group of patients will receive further consideration later.

Patients with local synthesis by isoelectric focusing (IEF)

Table 2 shows the categorization of all the patients by disease groupings, and the IEF patterns within each grouping. The largest single category of patients was MS with 206, or just over 20% of the total. The subcategories of MS will be considered later. Infections and the complications thereof (146), degenerative disorders (91), systematic disorders (71), neuropathies and myopathies (64) and psychiatric disorders (56) formed the bulk of the other patients. Of the 113 patients which fell into the 'other' category (Table 3), 101 had neurological diseases which could not be classified either because

TABLE 1. SUMMARY OF RESULTS OF IgG ANALYSIS FOR 1007 PATIENTS

	IEF	Log-Index	Both
Local synthesis	282	225	163
No local synthesis	725	782	663
Total	1007	1007	826

TABLE 2. BREAKDOWN OF ISOELECTRIC FOCUSING RESULTS BY PATIENT CATEGORIES

	Total	(+)	(>)	(*)	(P)	(-)
Congenital	4	0	0	0	0	4
Multiple sclerosis	206	181	5	1	0	19
Demyelinating—other	23	8	2	0	0	13
Vascular	39	0	0	3	0	36
Degenerative	91	0	0	4	1	86
Headache and pain	42	0	0	0	2	40
Infections and complications	146	44	11	9	0	82
Metabolic	12	0	0	0	0	12
Neuromyopathies	64	3	0	4	6	51
Paroxysmal	19	0	0	0	0	19
Neoplastic	35	5	1	6	1	22
Toxic	2	0	0	0	0	2
Trauma and sequelae	7	0	0	0	0	7
Skeletal and sequelae	44	0	0	0	4	40
Systematic	71	0	0	2	1	68
Psychiatric	56	0	0	0	0	56
Inflammatory	33	9	2	5	0	17
Other	113	10	1	2	2	98
Total	1007	260	22	36	17	672

(+) = local synthesis; (>) = local synthesis plus serum leakage; (*) = leakage of serum bands; (P) = paraprotein; (-) = no bands.

TABLE 3. BREAKDOWN OF PATIENTS IN THE 'OTHER' CATEGORY BY ISOELECTRIC FOCUSING

	Total	(+)	(>)	(*)	(P)	(-)
Uncertain—neurological	62	7	1	1	0	53
Myelopathy? cause	23	3	0	1	2	17
Certain—? cause	16	0	0	0	0	16
Uncertain—nonneurological	5	0	0	0	0	5
No disease found	7	0	0	0	0	7
Total	113	10	1	2	2	98

Abbreviations as in Table 2.

the cause of the disorder was unknown or the nature of the pathology was uncertain; in 12 patients no disease was found or a nonneuropathological disease suspected but no diagnosis could be made.

Table 4 itemizes all patients, apart from MS, in whom local synthesis of OCB in the CSF was found. In addition to demyelination, the majority fall into 2 categories: infectious and inflammatory disorders.

Patients with local synthesis by isoelectric focusing in categories other than demyelinating, infective or inflammatory

Fifteen patients were found in categories not traditionally associated with local synthesis of OCB, or fell into the 'other' diagnostic categories. Because of the clinical importance of defining the range of disorders associated with oligoclonal bands, and the need to assess accurately a false positive rate for the technique, we have tabulated these patients (Table 5), and have included clinical details here, so that the reasons for our conclusions may be more apparent.

One patient with a cerebellar syndrome was a 58-yr-old woman with no family history, an MRI scan showing cerebellar atrophy only and no plaques, and progressive weight loss. The weight loss had led to the suspicion of an occult malignancy and a resulting paraneoplastic syndrome, but at the time of lumbar puncture no evidence for such was apparent.

Three patients were described as suffering from dementia, but none was typical of a particular pathological type. The first was a 68-yr-old hypertensive male with a 6 yr history of progressive dysphasia, dysgraphia, slow mentation and somnolence but no memory loss. He was mildly dyslexic with a speech dyspraxia and preservation, a spastic dysarthria and bilateral extensor plantar responses. A computed tomographic (CT) scan showed atrophy only, and all other investigations were negative. Although he was clearly dementing there was no memory disturbance, and the presence of subcortical features makes a diagnosis of Alzheimer's disease questionable. The second was a 67-yr-old male with chronic obstructive airways disease requiring inhaled steroids. He was dementing, had an extrapyramidal syndrome and an acute confusional state resulting from sleep deprivation and pneumonia. His CT scan showed widespread cerebral and cerebellar involution, but a formal diagnosis could not be made. The third was a 40-yr-old male with a long psychiatric history and subsequently a dementing process with incontinence, spastic tetraplegia and dystonic limb posturing. A CT scan showed cerebral atrophy, an EEG was abnormal, and a muscle biopsy and white cells enzymes were unhelpful. No diagnosis could be made, but a novel disorder suspected.

One patient had a CNS tumour. This was a low grade glioma complicated by status epilepticus at the time of the lumbar puncture, and was the only CNS tumour with local synthesis of OCB. The relevance of the episode of status epilepticus was uncertain, as uncomplicated convulsive disorders are not associated with local synthesis of OCB, but encephalopathies are commonly associated.

Four patients had disorders for which no firm diagnosis could be made. A 35-yr-old male with 6 months of leg paraesthesiae, a 27-yr-old male with a year's history of an isolated brainstem lesion, a 43-yr-old female with bilateral weakness and paraesthesiae in the forearms and a 62-yr-old male with persistent pyrexia

TABLE 4. PATIENTS WITH LOCAL SYNTHESIS OF IgG BY IEF AND LOG-INDEX—MULTIPLE SCLEROSIS NOT INCLUDED

	<i>Total</i>	<i>IEF*</i>	<i>Index*</i>
Infections and complications			
Multiple cerebral abscesses	1	1	1
Pneumococcal meningitis	1	1	0
Meningitis	12	1 (8)	1 (8)
Subacute sclerosing panencephalitis	1	1	1
Herpes simplex encephalitis	5	4 (80)	3 (60)
Acute disseminated encephalomyelitis	10	5 (50)	3 (30)
Tropical spastic paraparesis	10	10 (100)	2 (20)
Lyme encephalitis	5	2 (40)	3 (60)
Other encephalitis, encephalopathy	56	19 (34)	17 (30)
Transverse myelitis	7	3 (43)	3 (43)
Neurosyphilis	9	7 (78)	2 (23)
HIV myelitis	2	1 (50)	0
Guillain-Barré syndrome	20	0	3 (15)
Other demyelinating disorders			
Optic neuritis	16	6 (38)	4 (25)
Demyelination ? cause	6	4 (67)	2 (33)
Inflammatory disorders			
Neuro-Behçet's disease	4	1 (25)	0
Wegener's granulomatous	1	1	1
Neurosarcoidosis	18	6 (33)	5 (28)
Stiff man syndrome	3	3 (100)	1 (33)
Neoplastic disorders			
Glioma, epilepsy, encephalopathy	1	1	0
Paraneoplastic syndromes	10	5 (50)	0
Spinal cord meningioma	2	0	1 (50)
Epidermoid	2	0	1 (50)
Degenerative disorders			
Cerebellar degeneration—sporadic	11	0	1 (9)
Cerebellar degeneration—hereditary	1	0	1
Spinocerebellar degeneration—sporadic	5	0	1 (20)
Spastic paraplegia—hereditary	1	0	1
Tremor—sporadic	2	0	1 (50)
Dementia	27	0	1 (4)
Neuropathies and myopathies			
Peripheral neuropathy	30	1 (3)	5 (17)
Cranial nerve lesions	17	2 (12)	0
Myasthenic syndrome	1	0	1
Vascular disorders			
Brainstem infarct	10	0	2 (20)
Sagittal sinus thrombosis	2	0	1 (50)
Anterior spinal artery occlusion	3	0	1 (33)
Spinal angioma	1	0	1
Headache and pain			
Migraine	12	0	2 (17)
Paroxysmal disorders			
Seizures	18	0	3 (17)
Toxic and postsurgical disorders			
Postsurgical CSF leak	1	0	1

Table 4 (*continued*)

	<i>Total</i>	<i>IEF*</i>	<i>Index*</i>
Uncertain diagnosis, cause unknown, no disease found			
Benign intracranial hypertension	9	0	4 (44)
Cervical myelitis ? cause	23	3 (13)	4 (17)
Syndromes involving dementia	2	2 (100)	1 (50)
Cerebellar syndrome	1	1	0
Paraesthesiae		2	1
Brainstem lesion		1	1
Pyrexia and cerebral disturbance	1	1	0
EEG abnormality and psychosis	1	1	0
Hydrocephalus	3	0	1 (33)
White matter lesions, ? nature	1	0	1
Neck pain	1	0	1
No disease found	7	0	4 (57)
Trauma and sequelae			
Radiation encephalopathy	1	0	1
Skeletal disorders			
Cervical spondylotic myelopathy	10	0	2 (20)
Psychiatric disorders			
'Functional' symptoms	45	0	5 (11)
Psychosis	11	0	3 (27)
Totals		96	104

* Percentages in parentheses

TABLE 5 18 PATIENTS IN WHOM OLIGOCLONAL BANDS WERE 'UNEXPECTED'

<i>Diagnosis</i>	<i>Log IgG-index</i>
Idiopathic cerebellar syndrome	0.55
Dementia, extrapyramidal syndrome	0.69
Dementia, extrapyramidal and pyramidal syndrome	1.25
Paraparesis, myelitis, neuropathy	1.05
Myelitis	1.23
Myelitis	1.02
Glioma, epilepsy	0.69
Inflammatory polyneuropathy	0.59
Sixth cranial nerve palsy	0.31
Multiple painful cranial nerve palsies	0.53
Leg paraesthesiae	0.58
Hand paraesthesiae and weakness	1.54
Brainstem lesion	1.01
Pyrexia, cerebral disturbance	0.64
EEG abnormality and psychosis	0.67

and evidence of cerebral dysfunction. In all of these many pathologies compatible with local synthesis of OCB could have been the cause.

Three patients had neuropathies. The first was a 25-yr-old male with an acute nonpainful sixth cranial nerve palsy and occipital headache. All other investigations, including CT scanning and angiography were normal, but it was felt possible that this was an atypical presentation of MS. An 88-yr-old female with progressive painful multiple cranial nerve palsies also had no other abnormalities on investigation, and a malignancy-related disorder seemed likely. The third was a 23-yr-old male with a subacute inflammatory

polyneuropathy atypical for the Guillain-Barré syndrome. His CSF cell count was markedly elevated but no other abnormalities were found and he improved spontaneously. None of the patients had serum examined for *Borrelia burgdorferi* antibody at the time of admission, since this preceded our awareness of its prevalence in the UK. In retrospect, however, this would have been an important investigation since the patient with the sixth nerve palsy was from a rural background, and the patient with the inflammatory polyneuropathy developed his illness while serving with the armed forces in West Germany.

A single patient with a psychiatric disorder had a long history of unipolar depression with recent onset delusional features and personality change. A malignant synovioma had been removed some years earlier. An EEG was grossly abnormal with spikes in both hemispheres, but there were no clinical features of epilepsy, and no clinical diagnosis could be made, although an encephalopathy was thought to have supervened.

In total, 15 patients appeared to fall outside accepted categories normally associated with local synthesis of OCB. If all these are considered to represent 'false' positives, this gives a 15/724 or all 2.0% false positive rate. However, as we have illustrated above 15 patients have disorders in whom the pathology had not been established, and considering these to be false positives is therefore unreasonable. This leaves no cases in which local synthesis can be said to be inconsistent with the clinical data, giving a false positive rate now of 0/724 or 0%. Of these 18 patients, 6 were also positive by the Log IgG-Index. Thus the true false positive figure probably lies between these extremes, and only long-term follow-up will yield the correct answer.

Patients positive for local synthesis by Log IgG-Index

Table 4 lists all the patients, apart from MS, positive by the Log IgG-Index. The distribution of positive results is similar in the major categories to that for IEF, but with smaller numbers within each group. Thus in addition to demyelination, infections and their sequelae formed the bulk of the patients with 39 positive patients. The remainder were fairly evenly and widely spread amongst the other diagnostic categories, with degenerative and psychiatric disorders being prominent and only the metabolic and systemic categories not being represented with positive results. A total of 54 patients with positive Log IgG-Indices fell into categories not normally expected to have local synthesis of IgG, giving a 'false' positive rate of 54/782 or 7.0%. As some of these patients overlapped with those described under the IEF results, and since IEF provides a standard by which to compare the Log IgG-Index results, we examined those patients in whom local synthesis was suggested by the Log IgG-Index but not corroborated by IEF.

Patients positive for local synthesis by the Log IgG-Index and negative by IEF

A total of 62 patients had local synthesis suggested by the Log IgG-Index but did not have local synthesis using IEF. These are listed in Table 6. In 53 of these patients a clear unequivocal diagnosis was obtained. In 9 either no disease was found (vertigo; hand pain; dysaesthesia with no objective findings) or no cause found for the disorder (benign muscle fasciculation; neck pain; sensory loss; cervical myelopathy, neuropathy and myelopathy; cerebral white matter lesions of uncertain nature). One patient had clinically definite MS, and this was the only MS patient identified by the Log IgG-Index in which OCB was negative.

Of these 62 patients, 9 were found to have serum IgG levels below the lower limit of our reference range (< 5 g/l). A total of 24 patients in our study population of 1007 (2.4%) had serum IgG below 5 g/l, which is what would be expected for a normally distributed population. However 10 of these were positive by the Log IgG-Index, which

TABLE 6 PATIENTS NEGATIVE FOR LOCAL SYNTHESIS OF IgG BY OLIGOCLONAL BANDING, BUT POSITIVE BY THE LOG IgG-INDEX

<i>Diagnosis</i>	<i>Number*</i>	<i>Serum</i> <i>< 5</i>	<i>IgG**</i> <i>> 5</i>	χ^2
Psychiatric	56	1	7	n.s.
Infections and complications	91	0	7	n.s.
Peripheral neuropathies	36	0	5	n.s.
Vascular	39	0	5	n.s.
Benign intracranial hypertension	9	0	4	< 0.001
No disease, nonneurological, ?cause	28	0	4	n.s.
Uncertain—neurological	54	1	4	n.s.
Guillain-Barré syndrome	20	0	3	n.s.
Neurosarcoidosis	12	1	2	n.s.
Degenerations	93	1	4	n.s.
Seizures	18	0	2	n.s.
Tumours	29	0	2	n.s.
Cervical spondylosis		1	1	
Headache		1	1	
Myasthenic syndrome		0	1	
Postsurgical CSF leak		0	1	
Radiation encephalopathy		1	0	
Dementia		1	0	
Multiple sclerosis—definite		1	0	
Totals		9	53	

** g/l, * Number in category without local synthesis of IgG by IEF

is much higher than would be expected by chance ($\chi^2 P < 0.05$). The index thus appears to be biased by hypogammaglobulinaemia. Conversely, only 1 patient with hypogammaglobulinaemia was positive by IEF, but there was no statistical association between presence of hypogammaglobulinaemia and absence of OCB. If these 9 patients with an artificially elevated Log IgG-Index are removed, 53 patients remain. As the index is a continuous variable, we subjected categories of patients to χ^2 analysis to see if any grouping was represented above that which would be expected by chance (Table 6). Only those patients with benign intracranial hypertension (BIH) had a statistically significant association with a positive Log IgG-Index ($P < 0.001$). The Log IgG-Index thus had a false positive rate of 62/782 or 7.9% using IEF as the standard. If those patients with hypogammaglobulinaemia and BIH are excluded the false positive rate drops to 49/768 or 6.4%. Even if those patients in whom no diagnosis could be made, together with those in whom a high index is a recognized association of the pathology are excluded, this still leaves 27/768 or 3.5% false positive rate. Interestingly, the single MS patient had hypogammaglobulinaemia, and so should be excluded from the Log IgG-Index results. This also means that both methods missed this patient, and there were therefore no patients with MS detected by the Log IgG-Index alone.

Comparison of isoelectric focusing and Log IgG-Index

Of the 282 patients with local IgG synthesis demonstrated by IEF, 163 (58%) were also positive by the Log IgG-Index (Table 1). This leaves 119 (42%) patients who would have been missed if the Log IgG-Index alone had been used. Even excluding those patients thought to represent false positives by IEF and who were negative by the Log IgG-Index (9 of the 15 patients in Table 5), 110 (39%) patients would be missed. Of the

225 patients positive by the Log IgG-Index, 62 were missed by IEF. If those 27 patients who were definite false positives by the Log IgG-Index are excluded, together with the 9 patients with hypogammaglobulinaemia, 26 patients would have been missed by the use of IEF alone. Further exclusion of those 22 patients in whom chance alone could have accounted for the positive index leaves only 4 patients missed by IEF.

It is impossible to establish true false negative rates for each method for the whole population, as there are very few diseases which have an invariable association with local IgG synthesis. It is possible, however, to take individual diseases or related groups and to compare the performance of the two methods. MS is the single most important group in which clinicians are interested, and we have therefore studied this in more detail, although we have also given consideration to some other categories where local synthesis was prominent.

Patients with multiple sclerosis

The performance of the Log IgG-Index and IEF in the detection of local synthesis of IgG in the subcategories of MS are shown in Table 7. Overall local synthesis of OCB was found in 90% of all patients, with patients classed as clinically definite MS having local synthesis of bands in 95% of cases. All other categories were positive in 86–89% of cases, with suspected MS and progressive probable MS the lowest at 86%.

The Log IgG-Index detected local synthesis in only 59% of patients overall. Clinically definite MS had the best detection rate at 67%, but there was a wide range of detection rates in the other categories with both categories of probable MS having the lowest positive rates at 45% for progressive and 53% for early probable or latent. Progressive possible and suspected MS were very similar at 56% and 59%, respectively.

Only 1 patient with MS was positive by the Log IgG-Index and negative on IEF. This patient had hypogammaglobulinaemia, and so should not be considered a true positive as described above. Conversely, 66 patients positive for local synthesis by IEF were missed by the Log IgG-Index. One patient with early probable or latent MS had a pattern of leakage of OCB from serum to CSF seen at 2 months after the onset of symptoms. The finding of serum bands in MS is not unusual, occurring in 2.4% of our patients, but its significance remains unknown. This patient went on to develop local synthesis on a further CSF analysis (not included in this study).

TABLE 7. ISOELECTRIC FOCUSING AND LOG IgG-INDEX IN MULTIPLE SCLEROSIS SUBCATEGORIES

Sub-category	No.	Isoelectric focusing						Index LS*
		(+)	(>)	(*)	(P)	(-)	LS*	
Clinically definite	82	77	1	0	0	4	78 (95)	55 (67)
Early probable or latent	64	54	2	1	0	7	56 (87)	34 (53)
Progressive probable	22	17	2	0	0	3	19 (86)	10 (45)
Progressive possible	9	8	0	0	0	1	8 (89)	5 (56)
Suspected	29	25	0	0	0	4	25 (86)	17 (59)
Totals	206	181	5	1	0	19	186 (90)	121 (59)

LS = local synthesis; for isoelectric focusing numbers equal the sum of (+) and (>); * Percentages in parentheses, other abbreviations as in Table 2

Other demyelinating diseases

Six of the 16 patients with isolated optic neuritis had local synthesis of oligoclonal bands; 4 were positive by the Log IgG-Index, and these were all positive by IEF, so that 2 patients were missed by the Index. As approximately 50% of patients with optic neuritis go on to develop MS, the outcome of those patients with oligoclonal banding will be of special interest.

Four of 6 patients with demyelinating disease of the central nervous system of unknown cause had local synthesis of oligoclonal bands, with 2 positive by the Index. One of the 4 had a disorder associated with lens dislocation without evidence of Marfan's syndrome or homocystinuria, and this patient also had serum bands.

Paraneoplastic syndromes

An unusual subgroup of patients was identified within the category of neoplastic disorders with paraneoplastic syndromes (Table 4). Of the 10 patients included, 5 had local synthesis of oligoclonal bands, 3 had serum leakage of bands and 2 were negative. The Log IgG-Index missed all 10 patients. There was no association between the type of paraneoplastic syndrome, or the primary tumour, and the type of IgG response. No other uncomplicated primary or secondary neoplasm was associated with local synthesis of oligoclonal IgG, so that the presence of local synthesis is highly predictive of paraneoplastic involvement rather than primary or metastatic disease ($\chi^2 P < 0.001$).

Infections and complications

This was the second largest patient grouping (Table 3), and also the second largest in number and proportion of patients with local synthesis identified by IEF and the Log IgG-Index with 55 and 37, respectively (Table 8).

TABLE 8 ALL PATIENTS WITH INFECTIONS AND COMPLICATIONS

<i>Diagnosis</i>	<i>Total</i>	<i>IEF*</i>	<i>Index*</i>
Multiple cerebral abscesses	1	1	1
Extradural abscess	1	0	0
Pneumococcal meningitis	1	1	0
Viral meningitis	2	0	0
Other meningitides	9	1 (11)	1
Subacute sclerosing panencephalitis	1	1	1
Herpes simplex encephalitis	5	4 (80)	3 (60)
Other specific encephalitis	1	0	0
Acute disseminated encephalomyelitis	10	5 (50)	1 (10)
Tropical spastic paraparesis	10	10 (100)	2 (20)
Lyme disease	5	2 (40)	3 (60)
Other postinfective complications	57	19 (33)	17 (30)
Transverse myelitis	7	3 (43)	3 (43)
Neurosyphilis	10	7 (70)	2 (20)
Malaria	1	0	0
Herpes zoster	1	0	0
Tuberculoma	2	0	0
HIV infection	2	1	0
Guillain-Barré syndrome	20	0	3 (15)
Totals	146	55	37

IEF = isoelectric focusing shows local synthesis, Index = Log IgG-Index shows local synthesis; * Percentages in parentheses.

Where a clearly identifiable single agent was the cause of the neurological disturbance, either a virus or bacterium, out of a total of 45 such patients 27 had local synthesis of oligoclonal IgG (60%), and 14 a positive Log IgG-Index (31%). Where no clearly identifiable single agent was found, or the disorder was a postinfective syndrome, only 28 had local synthesis of oligoclonal bands (28%), and 23 were positive by the Log IgG-Index (23%). All patients with tropical spastic paraparesis, 80% of patients with Herpes simplex encephalitis and 70% of patients with neurosyphilis had local synthesis of oligoclonal IgG. The single patient with Herpes simplex encephalitis negative in this study had the lumbar puncture within 5 days of onset of the illness and a subsequent analysis not included in this study was positive.

One particular postinfective complication, acute disseminated encephalomyelitis, had a 50% positive rate by IEF. Most significantly, no patient with the Guillain-Barré syndrome had local synthesis of OCB, although 5 (25%) had leakage of bands from the serum.

Diseases in which local synthesis of oligoclonal IgG is never found

Table 9 shows those groups of patients in whom local synthesis of OCB was never found, namely all patients with congenital neurological disorders, vascular disorders, headache and idiopathic pain syndromes, metabolic, paroxysmal, toxic and traumatic

TABLE 9 CATEGORIES OF PATIENTS IN WHOM LOCAL SYNTHESIS OF OLIGOCLONAL BANDS IS NOT FOUND

Categories in which bands are never found

- Congenital disorders
- Vascular disorders
- Headache and pain syndromes
- Metabolic disorders
- Paroxysmal disorders
- Toxic disorders
- Traumatic and sequelae
- Skeletal and sequelae including myelopathy
- Systematic disorders
- Psychiatric disorders
- Degenerative
 - Parkinson's disease
 - Autonomic failure
 - Alzheimer's disease and other dementias
 - Motor neuron disease
 - Spinal muscular atrophy
 - Hereditary degenerations
 - Idiopathic cerebellar, spinocerebellar degenerations

Categories in which bands are not found when complicating cases are excluded

- Neuropathies and myopathies
 - Peripheral neuropathies (hereditary and acquired)
 - Radicular syndromes
 - Isolated peripheral nerve lesions
 - Metabolic myopathies

Other groups in which local synthesis of bands is not found

- Isolated myelopathies
- Guillain-Barré syndrome
- Benign intracranial hypertension

disorders, skeletal disorders and their sequelae including myelopathy, and systemic and psychiatric disorders. Within other categories, some groups were also completely without local synthesis of OCB: Parkinson's disease, Alzheimer's disease and other uncomplicated degenerative dementias, motor neuron disease and spinal muscular atrophy, hereditary and idiopathic cerebellar and spinocerebellar degenerations, the Guillain-Barré syndrome and BIH. Peripheral neuropathies and isolated myelopathies, once patients already described in the text with complicated atypical manifestations or additional pathologies associated with local synthesis were excluded, had no local synthesis of OCB.

Patients with paraprotein patterns

Seventeen monoclonal gammopathies were identified on the basis of IEF, giving an incidence of 1.7% in our population (Table 3). In two groups a significant association was found with the presence of a monoclonal gammopathy: peripheral neuropathies with 5 of 38 patients ($\chi^2 P < 0.001$), and myelopathy of uncertain cause with 2 of 23 patients ($\chi^2 P < 0.001$). In no other diagnosis was any association found.

Patients with an excess of CSF bands over serum bands

Altogether 22 patients had a pattern of serum OCB leaking into CSF with additional locally synthesized OCB on IEF (Table 3). This was found in 5 of 206 patients with MS (2.4%), 2 of 23 patients with other demyelinating disorders (9%), 11 of 146 patients with infective or postinfective complications (7.5%) (including 2 of 10 patients with neurosyphilis and 4 out of 10 patients with tropical spastic paraparesis), and 1 patient each of neurosarcoidosis, paraneoplastic syndrome, the stiff man syndrome and encephalopathic convulsive disorder.

Leakage of oligoclonal bands into CSF

In 36 patients there was a pattern of leakage of OCB from the serum into the CSF, with no local synthesis of OCB (Tables 3, 10). These patients were scattered amongst many categories, and more importantly many of the patients had disorders in which the differential diagnosis would include demyelinating, inflammatory or infective processes. The 1 patient with MS and leakage of OCB from the serum and who has already been mentioned went on to develop locally synthesized OCB. The patient with myasthenia gravis had a malignant thymoma with multiple metastases, and it is these that are the likely origin of the oligoclonal bands leaking from serum.

Predictive value of isoelectric focusing

Table 11 summarizes the probability of any CSF and serum pair from a patient when received by our laboratory falling into a particular diagnostic category when IEF suggests local synthesis of IgG. For comparison the predictive value for the Log IgG-Index is also included. Before any test is performed, the chances of a given sample being from a patient in a particular disease category (prior probability) can be estimated by simple proportions. For MS this is 0.20. If IEF shows local synthesis of IgG, the probability that the patient has one of the categories of MS rises to 0.66. Similarly the prior probability for a sample coming from a patient with an infective disorder is 0.14, but if IEF shows local synthesis this probability rises to 0.20. Notably, the chances of a positive IEF result being in any other given category is less than 0.04 at best, and nil for many

categories, despite the prior probabilities being much higher. The Log IgG-Index performed much less well for demyelinating and infectious disorders at 0.53 and 0.16 respectively, and gave higher probabilities for most other categories, reducing its discriminatory value considerably.

TABLE 10. PATIENTS WITH LEAKAGE OF OLIGOCLONAL BANDS FROM SERUM INTO CSF

<i>Diagnosis</i>	<i>Number</i>
Multiple sclerosis	1
Cerebral infarct	3
Steele-Richardson-Olszewski syndrome	1
Familial cerebral degeneration	1
Familial cerebellar degeneration	1
Alzheimer's dementia	1
Guillain-Barré syndrome	5
Extradural abscess	1
Meningitis	1
Encephalitis	1
Postinfective encephalomyelitis	1
Peripheral neuropathy	3
Myasthenia, thymoma, metastases	1
Paraneoplastic	3
Epidermoid	1
Calcified intracranial mass	1
Spinal metastases	1
Sturge-Weber syndrome	1
Optic neuropathy	1
Temporal arteritis	1
Mixed connective tissue disorder	1
Neurosarcoidosis	3
Pontine lesion ?cause	1
Myelopathy ?cause	1
Total	36

TABLE 11. PREDICTIVE VALUE OF AN INDIVIDUAL PATIENT FALLING INTO A PARTICULAR DIAGNOSTIC CATEGORY IN RELATION TO LOCAL SYNTHESIS OF IgG DETERMINED BY ISOELECTRIC FOCUSING

<i>Category*</i>	<i>Prior probability</i>	<i>IEF positive</i>	<i>Index positive</i>
Multiple sclerosis	0.20	0.66	0.53
Infections and complications	0.14	0.20	0.16
Demyelinating—other	0.02	0.04	0.03
Other	0.11	0.04	0.08
Inflammatory	0.03	0.04	0.03
Neoplastic	0.03	0.02	0.01
Neuromyopathy	0.06	0.01	0.03

* Only those categories containing patients with local synthesis of IgG as defined by IEF are included.

DISCUSSION

Since the first identification of the abnormal nonheterogenous nature of the IgG response in the CSF 30 years ago (Karcher *et al.*, 1957; Boij, 1958), and its designation as

oligoclonal (Laterre, 1965), a number of methods have been developed for the detection of such bands. Agar gel electrophoresis formed the basis of the seminal work in this field (Lowenthal *et al.*, 1960), where bands were identified in a number of diseases such as neurosyphilis, trypanosomiasis, subacute sclerosing panencephalitis and MS. In MS, agar gel electrophoresis identified oligoclonal bands in about 80% of cases (Laterre *et al.*, 1970), but also in a number of disorders where immune abnormalities would not be expected. The concentration of CSF, and the failure to run serum in parallel in early studies may have underlain some of these problems. Agarose gel electrophoresis became available in the 1970s, with up to 100% of clinically definite cases of MS reported as showing oligoclonal bands (Johnson *et al.*, 1977), but again concentration of CSF was necessary before running, and artefactual bands present in the gamma globulin region made interpretation difficult (Laurenzi and Link, 1978). A comparison of the two methods of agar and agarose electrophoresis yielded similar percentages of positive results in MS (95 and 98%, respectively), but agarose yielded a much higher number of positive CSF results in patients without CNS immune disorders (Link, 1973). Cellulose acetate electrophoresis, although showing a homogenous increase in the gamma globulin area in 90% of MS patients, showed only a few with oligoclonal banding, and when compared with agarose was far less efficient (Vandvik and Skrede, 1973). Polyacrylamide gel electrophoresis yielded oligoclonal bands in up to 90% of MS patients (Thompson *et al.*, 1979), and was more sensitive than cellulose acetate (Goodland and Thompson, 1983), but was far more laborious and thus unsuited to routine laboratories.

Isoelectric focusing, which has much greater separating capacity than electrophoresis, when applied to concentrated CSF on polyacrylamide gels, showed oligoclonal bands in up to 95% of MS patients (Sidén and Kjellin, 1978), and was far superior to agarose gel electrophoresis in MS (95% vs 65%, respectively; Delmotte and Gonsette, 1977). The prerequisite for concentration of CSF, and the resultant artefacts led to the search for an alternative medium. Agarose IEF of unconcentrated CSF with specific immunofixation for IgG has proved better than agarose electrophoresis in the detection of oligoclonal bands in MS (100% versus 94%, respectively), and in the ease of interpretation (Kostulas, 1985). Indeed Kostulas in his monograph has published one of the largest series of patients studied with agarose IEF, and although his positive rate for MS was 100%, there was a high proportion of positive results in other disease groups in which an associated immunological disturbance, such as cerebrovascular disease (11%), Parkinson's disease (14%), dementia (7%) and psychoneurosis (10%) would not normally be anticipated. Although our laboratory has also found agarose IEF to be the best method for detection of oligoclonal bands (Walker *et al.*, 1983), we have not found local synthesis in such a wide variety of diseases. This may be due to a combination of differences in the sensitivities of differing methods, in the criteria used to define local synthesis and in the patient populations from which samples were drawn. Part of our study has thus been to address this question of the range of diseases associated with local synthesis of oligoclonal IgG. The debate over the use of quantitative versus qualitative measurements of IgG has been far less clearly defined, and the development of a succession of formulae to calculate intrathecal IgG synthesis has made comparisons difficult. There have been several previous studies comparing oligoclonal banding of IgG and quantitative analysis in the assessment of local synthesis of IgG within the intrathecal compartment of the CNS (Olsson and Pettersson, 1976; Laurenzi and Link,

1978; Poloni *et al.*, 1979; Perkin *et al.*, 1983). The majority of the studies have used relatively insensitive methods for detection of oligoclonal bands, such as polyacrylamide gel separation and silver staining, and so have not come down clearly in favour of one or other method. The advent of the more sensitive technique of IEF with specific immunostaining, and the continuing debate over the issue, led us to attempt a resolution in our own laboratory.

We have come down firmly in favour of IEF as the best method by far for detecting abnormalities of IgG in the CSF of patients with neurological disorders. It detected local synthesis of IgG in 282 of the 1007 patients, with no false positives; 4 patients were missed in whom local synthesis of IgG was found by the Log IgG-Index. The index performed poorly overall in comparison, identifying 225 patients with local synthesis of IgG, with a false positive rate of 3.5%, and 110 patients missed which had local synthesis by IEF.

As we have seen, hypogammaglobulinaemia falsely skews the results, giving higher indices than would be expected. This suggests that there is a nonlinear relationship between the IgG ratio and albumin ratio especially at low serum IgG values. Indeed, it has even been suggested that the relationship between serum and CSF IgG is nonlinear at any level, and in fact is a random association. The majority of studies using formulae do not take this bias induced by hypogammaglobulinaemia into account, which may partially explain their poorer clinical correlation and the high number of false positive results, as seen in our study. Taken together with the necessary analytical errors in calculating 4 separate parameters, it is not therefore surprising that quantitative formulae do not perform as well as qualitative analyses. It is thus vital that investigators become aware of those shortcomings in the use of formulae, and exclude those patients from their analyses.

There was a small group of patients who were positive both by IEF and by the Log IgG-Index, but who fell into categories not normally associated with local synthesis of IgG (Table 5). These 6 individual cases were discussed at length in the results section when considering the false positive oligoclonal band results. All 6 patients had reasonable alternative explanations for local synthesis.

The significant association between local synthesis of IgG by the LogIgG- Index and benign intracranial hypertension (BIH) is unexpected. BIH is still of unknown aetiology, although research has focused on mechanical considerations of CSF production and circulation. Immunological mechanisms have not been considered in the pathophysiology, but this finding would suggest that such an avenue would be fruitful. The finding of a significant association of local synthesis of oligoclonal IgG and the stiff man syndrome, however, supports previous reports (Meinck and Ricker, 1987; Solimena *et al.*, 1988). In addition, Solimena *et al.* demonstrated local synthesis of antiglutamic acid decarboxylase antibodies in the CSF of their single case, and postulated that the disease represents an autoimmune disorder. Whether the oligoclonal bands of IgG represent these specific autoantibodies remains to be established.

It must be emphasized that the population of patients that we have used is not typical of that likely to present to the average neurological department. Although we are a primary referral centre, we are also a major secondary and tertiary centre, and as such will have a higher proportion of rare, unusual and atypical cases. This has two main effects on our patient population: the proportion of patients with 'common' neurological disorders

will be reduced, but their absolute numbers will still be representative of our local population, and the proportion of patients with unclassifiable diseases will be high since by the mere fact that they are tertiary referrals, there is an implication of diagnostic difficulty. The effects of these on our results will be to bias our false negative and false positive rates by having so many rare and difficult cases, thus making our figures likely to represent the worst extreme seen in the population. There will also be a lowering of the efficiency of the predictive value of our results compared with a less selected population. So saying, these effects will be equal for the two methods studied, and thus the superiority of IEF over the Log IgG-Index will still be present in any other population studied. It also makes the diagnostic yield for OCB in individual disease groups, such as MS all the more significant.

One further major difficulty in assessing the results of immunological studies on neurological populations is the unintentional bias of the clinicians in the presentation of samples to the laboratory. Paired samples are only likely to be sent for analysis in most neurological centres if there is already a suspicion that the result is going to be abnormal; if the clinician is reasonably confident about a diagnosis, or is seeking only limited information such as microbiological analysis in meningitis, a serum sample is unlikely to be forthcoming and the CSF may never be referred for immunological studies. We have hoped to circumvent this in our hospital by running a service on all CSF samples sent to the pathology department including immunological analysis whether requested or not. This has the advantage of allowing us to study a much wider range of neurological diseases than any other study has been able to do so far, yielding associations not previously recognized and allowing us to reject immunological abnormalities previously reported in isolated cases as being spurious. It also makes our study far more representative of the spectrum of neurological disease as a whole, and not just immunologically mediated disorders. Nevertheless, some selective bias must still remain.

Care must always be taken in retrospective analyses of drawing too many conclusions about small numbers of patients generated by subgroup analysis. Thus although one should be aware of the association between local synthesis of IgG and BIH, one should be sceptical until a separate prospective study is performed looking at each group as a whole. In a similar fashion one must also be careful in the use of diagnostic categorizations, which may be artificial, and often do not have provision for multiple pathologies. It is this problem which we have attempted to avoid by itemizing the diagnosis of patients wherever possible within broad categories and where complex cases occurred, but inevitably there were still patients who did not lie happily within their diagnosis and perhaps should have been classified amongst the 'other and unknowns'.

The most important part of this discussion should be addressed to the clinicians, who wish to know how useful a test local synthesis of oligoclonal IgG is going to be in clinical practice. In this study, if the result is positive, and no clinical information is taken into consideration, then there is a 2 in 3 chance that the patient has MS, and a 1 in 5 chance of an infection or postinfective disorder. There will be very few cases in which the differential diagnosis on any given patient is going to include all possible causes of oligoclonal banding. Thus in practice if the clinician is interested in MS as the possible diagnosis, those diseases should be excluded, leaving a much higher predictive value for the test.

In MS, as a laboratory corroborative test, IEF for oligoclonal IgG performs very

well, with 95% of all clinically definite cases being positive, and 90% overall in all categories. Of particular note is the high positive rate in the suspected MS group at 86%. We cannot perform a direct comparison with other diagnostic investigations, such as MRI or evoked potentials, as this was not the aim of the study, and these investigations, although performed in many of the patients, would not have been subject to the same selection criteria and investigator independence in a retrospective study. We can say that in our hands OCB analysis performs better than evoked potentials reported in other studies (Bartel *et al.*, 1983; Hutchinson *et al.*, 1983; Ganes *et al.*, 1986) and in the main as well as MRI (Gebarski *et al.*, 1985; Cutler *et al.*, 1986; Farlow *et al.*, 1986; Guérit and Argiles, 1988), with few exceptions (Ormerod *et al.*, 1987). In the context of MRI studies, it has been pointed out that in many the diagnosis has been established or suspected before the investigation and the results of the studies cannot therefore be extrapolated to other clinical settings in which MRI is performed (Paty *et al.*, 1988). Most comparative studies have not used the most up-to-date methods of electrophoresis, and so comparisons of the two techniques have been unfair and not now of relevance. Where comparable methods have been used in the diagnosis of clinically definite MS, there has been little to choose between MRI, evoked potentials and IEF of CSF (Guérit and Argiles, 1988). There are also few prospective trials evaluating the role of the three major diagnostic aids. From a practical point of view, for those clinicians who only have access to evoked potentials and IgG analysis, and with the performance of oligoclonal banding being almost equal to MRI, this must be the obvious choice.

Oligoclonal banding is not discriminatory for individual diseases but when positive, can be used to exclude diseases which we have established as having no association with local synthesis of IgG as illustrated in Table 11. Thus if local synthesis is found in any of these, the clinician should be alerted to the likelihood of an alternative diagnosis. The absence of local synthesis does not exclude any particular diagnosis but again should alert the clinician to other diagnostic possibilities, especially in those disorders where the vast majority of patients are positive such as MS. An additional small bonus in our study was the finding that the presence of local synthesis of oligoclonal IgG in patients with tumours and neurological disturbance is more likely to represent paraneoplastic immunological involvement than direct tumour invasion.

The importance of using matched CSF and serum samples cannot be over-emphasized. Serum OCB can arise from any systemic stimulation, such as an intercurrent infection, and will leak into CSF. In our 36 patients with such a pattern, the examination of the CSF alone would have been entirely misleading in those cases where the differential diagnosis was important, such as the patients with neurosarcoidosis, degenerative syndromes, connective tissue disorders and myelopathies, all of which can be confused with MS. Monoclonal patterns are not only found from serum leakage but may also be a feature of CNS lymphomas and regularly appear in the early phase of CNS infections. The running of matched CSF and serum is thus essential here, and the increased sensitivity of the technique over conventional electrophoresis may give an additional diagnostic bonus.

In summary, our study shows that the analysis of CSF for local synthesis of IgG is of immense value, particularly in the demyelinating disorders such as MS, where as an adjunct to clinical examination it ranks alongside MRI in diagnostic precision. The method of choice is IEF for the detection of oligoclonal IgG, and we would not

recommend the further use of the formulae, especially not as a screening procedure. The simplicity of IEF, and its ready availability to most clinicians should make it a prominent investigation in the management of patients not just with suspected demyelination, but in a variety of other disorders, where a negative result may be just as helpful. We do not suggest that it be used as a screening tool for all patients with suspected neurological disorders, but propose that it should be used more extensively than is the case to date.

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CONGENITAL MYASTHENIA ASSOCIATED WITH FACIAL MALFORMATIONS IN IRAQI AND IRANIAN JEWS

A NEW GENETIC SYNDROME

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SUMMARY

Fourteen Jewish patients from 10 families of either Iraqi or Iranian origin with congenital myasthenia had associated facial malformations which included an elongated face, mandibular prognathism with class III malocclusion and a high-arched palate. Other common features were muscle weakness restricted predominantly to ptosis, weakness of facial and masticatory muscles, and fatiguable speech; mild and nonprogressive course; response to cholinesterase inhibitors; absence of antibodies to acetylcholine receptor; decremental response on repetitive stimulation at 3 Hz but no repetitive compound muscle action potential in response to a single nerve stimulus. This newly recognized form of congenital myasthenia with distinctive ethnic clustering and associated facial malformations is transmitted as an autosomal recessive disorder. The facial abnormalities may be secondary to the neuromuscular defect or may be primary and unrelated. Further studies are needed to elucidate the defect in neuromuscular transmission responsible for the pathogenesis of this syndrome.

INTRODUCTION

Congenital myasthenia is a hereditary disorder of neuromuscular transmission, with the onset of symptoms at birth or shortly thereafter (Fenichel, 1978). It encompasses several distinct syndromes (Engel *et al.*, 1981), sharing a few common features, including a typical distribution of the muscle weakness, mild symptoms with little or no progression over the years, and no immune mechanism involvement in the pathogenesis. Most of the reports published so far have described small numbers of cases in various ethnic groups (Namba *et al.*, 1971).

Facial skeletal abnormalities have long been known in several neuromuscular diseases, such as myotonic dystrophy and various congenital myopathies. Patients with central core disease, nemaline myopathy, centronuclear myopathy and congenital fibre type disproportion frequently have an elongated head in the anteroposterior direction, a long and narrow face, high-arched palate and dental malocclusion (Engel and Banker, 1986). To date such facial deformities have not been described in association with congenital myasthenia.

We have recently examined 14 patients with unique clinical features that, in our opinion,

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constitute a distinct and hitherto unrecognized syndrome in the spectrum of congenital myasthenia. These features are (1) clustering in a specific Oriental Jewish ethnic group, and (2) association with facial malformations, namely long face, high-arched palate, mandibular prognathism with malocclusion and open bite. The purpose of this report is to give a detailed account of the clinical and genetic findings in this disorder.

CASE REPORTS AND FAMILY STUDIES

The cases are summarized in Table 1. The symbols in brackets refer to the pedigrees given in fig. 1.

Case 1 (A IV 1)

This male patient was referred for neurological evaluation at the age of 24 yrs. He was then a candidate for surgery for mandibular prognathism, and neurological consultation was requested because of ptosis and difficulties in mastication. He was born in Israel to parents of Iranian origin. The parents were first cousins. From the age of 1.5 yrs, the patient was known to have bilateral ptosis. Since childhood he noticed gradual weakening of his voice during prolonged speech. There was no difficulty in swallowing or easy fatigability of limb muscles. The patient's condition remained stable until adulthood. A sister, and maternal

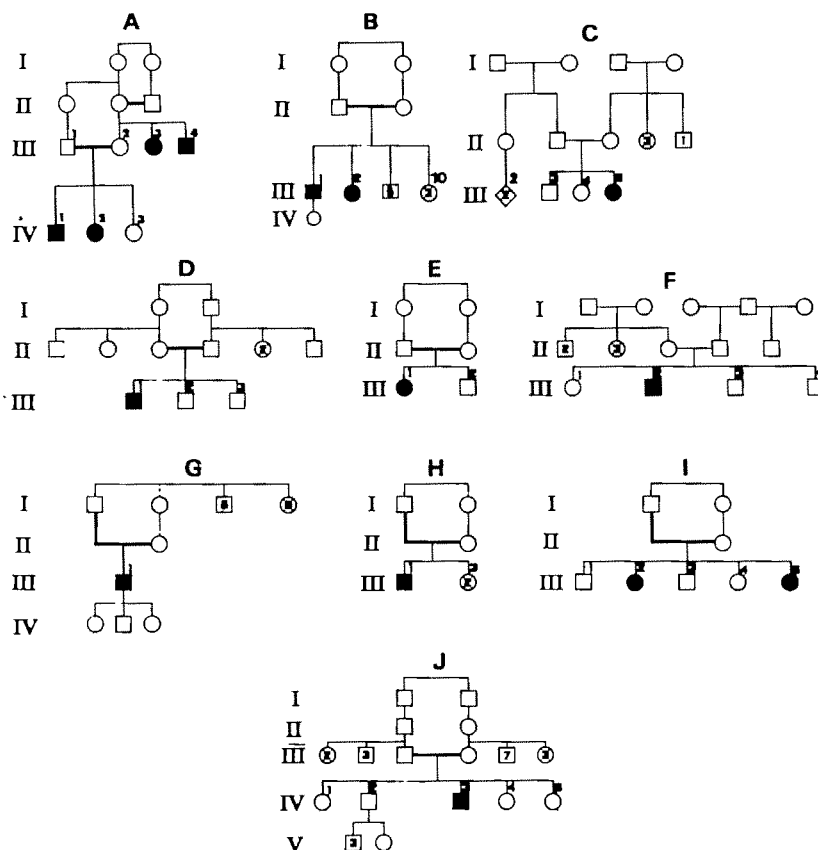


FIG. 1. Pedigrees.

TABLE 1 CLINICAL CHARACTERISTICS OF 14 PATIENTS WITH CONGENITAL MYASTHENIA

Case	Age at diagnosis (yrs)	Ethnic origin	Consanguinity	Other cases in family	Tensilon test	Decremental EMG response	ACHR antibodies	Thymoma	Surgery for myasthenia	Treatment
1	24	Iran	+	+	+	+	-	-	+	Pyridostigmine
2	15	Iran	+	+	+	-	-	-	-	Pyridostigmine
3	42	Iran	+	+	+	+	-	-	-	None
4	9	Iran	+	+	+	+	-	-	+	Pyridostigmine
5	18	Iran	+	+	+	-	-	-	-	Pyridostigmine
6	2	Iraq	-	-	+	+	-	-	-	Pyridostigmine
7	3	Iraq	+	-	+	n.d.	-	-	-	Pyridostigmine
8	9/12	Iraq	+	-	+	+	-	-	-	Pyridostigmine
9	9	Iraq-Turkey	-	-	+	+	-	-	-	Pyridostigmine
10	40	Iraq	+	-	+	+	-	-	+	Pyridostigmine
11	24	Iran	+	-	+	n.d.	-	-	+	Pyridostigmine
12	7	Iran	+	+	+	n.d.	-	-	-	Pyridostigmine
13	19	Iran	+	+	+	n.d.	-	-	-	Pyridostigmine
14	32	Iran	+	-	+	+	-	-	-	Pyridostigmine

n.d. = not done.

aunt and uncle had similar symptoms. Another sister, both parents and the rest of the family were asymptomatic.

On examination, several dysmorphic facial features were noted. The patient had a very elongated, protruding mandible; malocclusion; crowding of the teeth; a very high-arched palate; and facial asymmetry with the left side higher than the right. Neurological examination revealed severe bilateral ptosis with fatigue phenomenon; moderate weakness of the orbicularis oculi; mild weakness of the neck muscles; pseudointernuclear ophthalmoplegia with diplopia on left lateral gaze after repeated saccades. His speech showed mild fatigability. Limb muscle strength was normal. A Tensilon test was positive, with complete disappearance of the ptosis and diplopia, and improvement in speech and orbicularis oculi power. Repetitive stimulation of the right accessory nerve at a rate of 3 Hz produced a decremental response of 13% in the trapezius muscle. After injection of 10 mg edrophonium and a positive clinical response, the decrement was reduced to 7%. There was no repetitive firing of the muscle in response to a single nerve stimulus. A chest x-ray was normal and there were no antibodies to acetylcholine receptors (AChR) in the serum.

Treatment with pyridostigmine, 60 mg thrice daily, produced significant but incomplete improvement. As some degree of ptosis remained, and increased doses of pyridostigmine produced muscarinic side effects, the ptosis was treated surgically. For cosmetic reasons and in order to improve mastication, he later underwent surgical repair of the facial deformity, with two-piece maxillary osteotomy followed by bilateral oblique mandibular osteotomy.

The patient continues to take pyridostigmine and has remained in a good and stable functional condition with no signs of progression over a follow-up period of 3½ yrs.

Case 2 (A IV 2)

This patient is the younger sister of Case 1 and was first examined by us at the age of 15 yrs. Since the age of 2 yrs she had had bilateral ptosis, easy speech fatigability, and some difficulty in chewing hard foods. She did not seek medical attention for these symptoms until her brother was seen in our clinic.

On examination she had an elongated face (although less elongated than in her brother), mandibular prognathism, open bite and a high-arched palate. Neurological examination revealed marked bilateral ptosis, moderate weakness of the orbicularis oculi, mild weakness of the neck flexors and muscles of mastication, and mild fatigability of speech. A Tensilon test was positive, with disappearance of ptosis and orbicularis oculi weakness. Repetitive stimulation of the accessory nerve at a rate of 3 Hz produced no decremental response. Two min after voluntary effort a mild decremental response was observed, which was still within normal limits. Serum AChR antibodies were not found. The patient's symptoms have improved with pyridostigmine, 60 mg thrice daily.

Case 3 (A III 4)

This patient, a maternal uncle of Cases 1 and 2 (fig. 2) was examined by us at the age of 42. He was born in Iran and his parents were also first cousins. He shared with the first two patients an elongated face, a high-arched palate and mandibular prognathism. Neurological examination revealed bilateral ptosis with fatigue phenomenon, mild weakness of the orbicularis oculi and neck muscles, and easy speech fatigability. A Tensilon test was positive. Repetitive stimulation produced a significant decremental response. He chose not to take any medication. His sister, a maternal aunt of Cases 1 and 2 (AIII 3) was also reported by her relatives to have bilateral ptosis, difficulties in speech and mastication, and a jaw deformity. She could not be persuaded to seek medical attention for these symptoms.

Case 4 (B III 1)

This male patient was the product of a consanguineous marriage between first cousins of Iranian origin. He was noted from birth to have bilateral ptosis. Swallowing was normal, but since infancy difficulties in mastication appeared and weakness of the facial musculature was found. A younger sister (Case 5) had similar symptoms, though milder. Eight other siblings (5 brothers and 3 sisters) and both parents were normal.

A diagnosis of hereditary myasthenia was made and therapy with pyridostigmine was started at the age of 9 yrs. His condition has remained stable since then. At the age of 22 he underwent surgery for mandibular prognathism with malocclusion. Bilateral mandibular osteotomy and intermaxillary fixation were performed. Examination at our clinic at the age of 33 revealed scoliosis, a high-arched palate, bilateral ptosis with fatigue phenomenon, marked weakness of the orbicularis oculi and the rest of the facial musculature, and mild weakness of the muscles of mastication. The patient also complained of easy fatigability of speech

and limb muscles, but no weakness. Repetitive stimulation of the accessory nerve produced a decremental response of 10.7% in the trapezius muscle. After Tensilon injection there was no change in the decremental response, despite marked clinical improvement in the ptosis and facial weakness. No repetitive muscle firing was seen in response to single nerve stimuli. A chest x-ray was normal, and serum AChR antibodies were not found. The patient is currently taking pyridostigmine in small doses, and holds an administrative job. On occasions he has tried to discontinue the medication, but recurrence of ptosis and facial weakness has compelled him to resume it.

Case 5 (B III 2)

A younger sister of Case 4, this patient has had bilateral ptosis since birth, with marked worsening in the evenings. She has also had difficulty in mastication since infancy. After prolonged speech her voice becomes weak and nasal. She has no symptoms relating to the limb muscles, and is a good athlete. Her condition has remained almost unaltered since childhood, with some deterioration in the masticatory muscles. Examination at the age of 18 yrs revealed moderate bilateral ptosis with fatigue phenomenon; weakness of the orbicularis oculi and other facial muscles; pronounced weakness of the masseters; mild speech fatiguability. Her face was not elongated, but she had a high-arched palate and an open bite. A Tensilon test was positive, resulting in disappearance of the ptosis and improvement in power of the facial and masticatory muscles. Repetitive stimulation of the accessory nerve at 3 Hz produced no decremental response. No repetitive muscle firing was seen in response to single nerve stimuli. Immediately following effort, and 2 min later, no change was noted. Repetitive stimulation of the facial nerve and recording from the orbicularis oculi produced a decremental response of 6% (within normal limits). The serum CK was normal, and serum AChR antibodies were not present. The patient has been treated with pyridostigmine according to need, with good clinical response. Medication is beneficial for speech and masticatory function, and improves the ptosis and facial weakness.

Case 6 (C III 5)

This female patient is the daughter of parents of Iraqi origin, with no consanguinity. At the age of 2 months she had feeding problems due to easy fatiguability on sucking. Other abnormalities noted at the same time included a weak cry, bilateral ptosis and mandibular prognathism with malocclusion. When she started to walk, she had a waddling gait that soon became normal. A Tensilon test at the age of 2 yrs was positive, and treatment with pyridostigmine was started, with good but incomplete response. There has been no progression of the disease since then.

On examination in our clinic at the age of 10.5 yrs, we found a normally developed girl with marked bilateral ptosis and fatigue phenomenon, a drooping jaw, severe weakness of the facial musculature, dysarthria with nasal speech, and weak neck flexors. All other muscles were normal. She had a high-arched palate and mandibular prognathism with malocclusion. A Tensilon test showed complete disappearance of the ptosis. On repetitive stimulation of the accessory nerve at a rate of 3 Hz, a decremental response of 8% was found. Immediately after voluntary effort there was no change, but 2 min later the amplitude decreased, with a decremental response of 10%. After Tensilon the response was unchanged. No repetitive muscle firing was recorded in response to single nerve stimuli. A chest x-ray was normal, and there were no serum AChR antibodies. The patient has 2 healthy siblings, and no other cases of the disease are known in the family. She takes pyridostigmine and is currently undergoing orthodontic treatment for malocclusion.

Case 7 (D III 1)

This male patient was born to parents of Iraqi origin, who were first cousins. During the first year of life he had frequent severe respiratory infections. When he was 1 yr old he had a severe aspiration episode, and tracheostomy was performed. At the age of 3 he was found to have bilateral ptosis, a drooping jaw and a weak voice. A Tensilon test was positive, and a diagnosis of myasthenia gravis was made. A chest x-ray showed a normal thymus, but the patient nonetheless underwent thymectomy, with no clinical improvement. EMG then was reported as normal. The course of the disease was stable, with no further progression. On examination in our clinic at the age of 21, we found bilateral ptosis with fatigue phenomenon, mild weakness of the masticatory muscles, moderate weakness of the orbicularis oculi and other facial muscles, mild dysphagia for solids and fluids, and fatiguable speech. He also had mandibular prognathism with an open bite, and a high-arched palate. The patient refused an EMG examination and was not interested in a surgical procedure for prognathism. He manages well on pyridostigmine, 60 mg thrice daily. There

are no other cases of the disease in his family. One of his 4 brothers died at the age of 1.5 yrs, reportedly following a penicillin injection; no other data were available.

Case 8 (E III 1)

This female patient is the product of a consanguineous marriage between first cousins, of Iraqi origin. At the age of 9 months she was admitted to hospital because of severe bronchopneumonia, and during her disease several episodes of aspiration occurred. At first no other abnormalities were found on examination, but one evening ptosis was observed, and it was then noted that every evening she developed bilateral ptosis and an expressionless face. A Tensilon test was positive, and pyridostigmine treatment was started. The disease has had a stable course, and aspirations did not recur after infancy.

On examination in our clinic at the age of 30 yrs, the following abnormalities were found: moderate bilateral ptosis with fatigue phenomenon, moderate weakness of the orbicularis oculi and other facial muscles, mild weakness of the masticatory muscles, a nasal voice and mild fatiguability with prolonged speech. All other muscles were normal. The patient had marked elongation of the face with mandibular prognathism

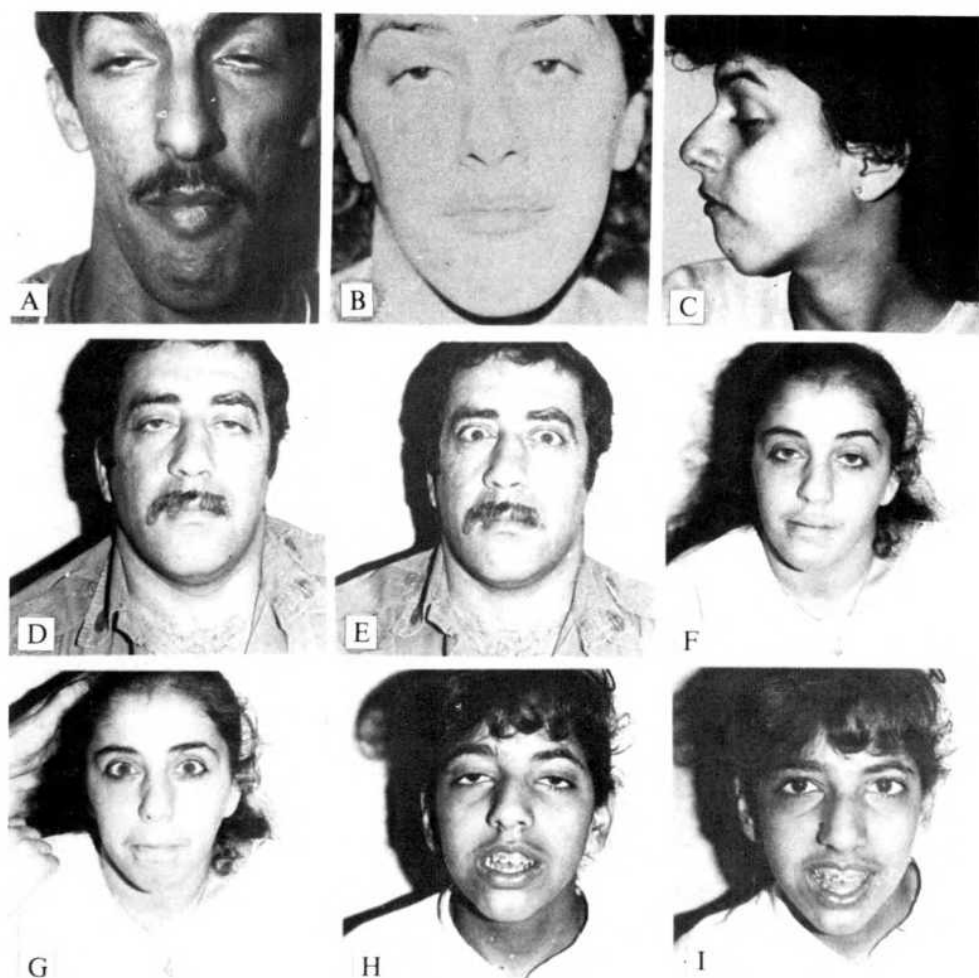


FIG. 2A-I.

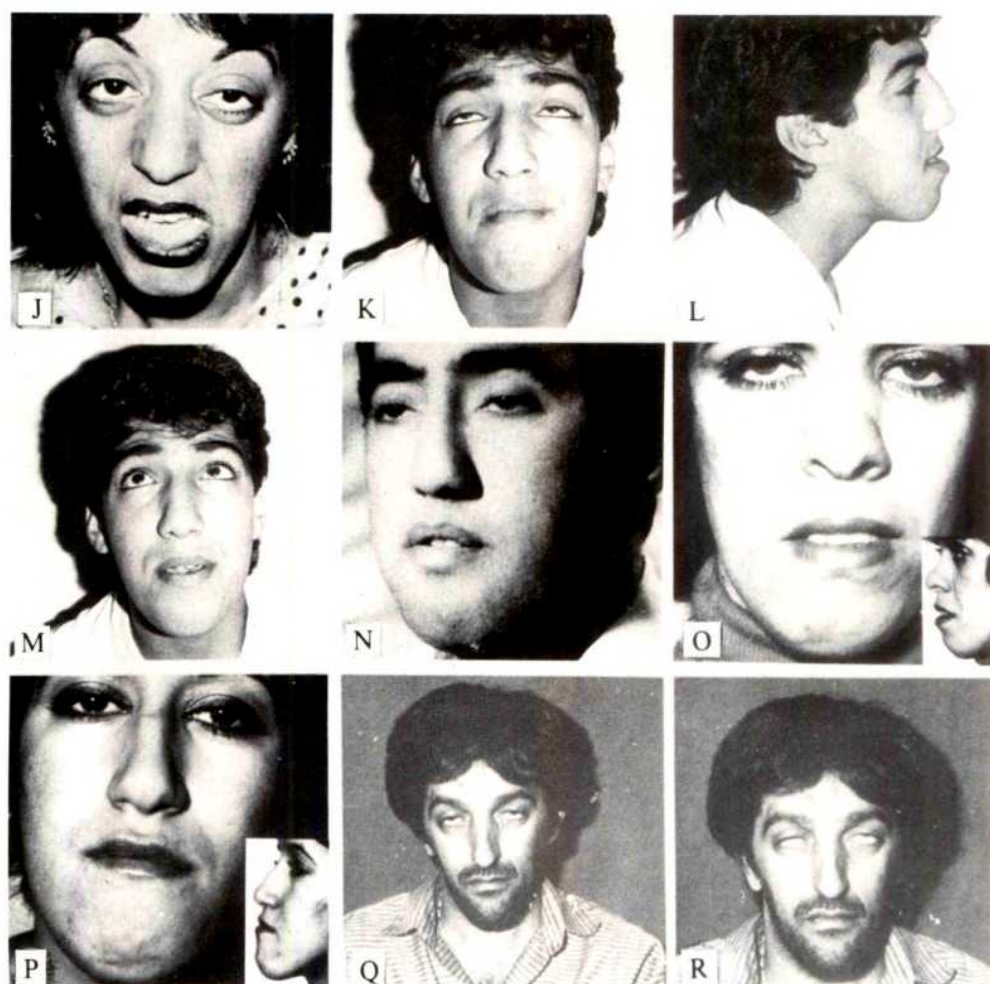


FIG. 2. A, Case 1 (A IV); B, C, Case 2; D, E, Case 4, before and after Tensilon (following mandibular surgery); F, G, Case 5, before and after Tensilon; H, I, Case 6, before and after Tensilon; J, Case 8; K, L, M, Case 9, before and after Tensilon; N, Case 10; O, Case 12; P, Case 13; Q, R, Case 14.

and malocclusion, and a high-arched palate. A Tensilon test was positive, with disappearance of the ptosis and improvement of orbicularis oculi power. Repetitive stimulation of the accessory nerve at a rate of 3 Hz produced a decremental response of 13%. Following an injection of Tensilon the amplitude increased by 25%, resulting in a decrement of only 7%. A chest x-ray and serum CK were normal, and there were no serum AChR antibodies. The patient has been treated with pyridostigmine, 60 mg thrice daily, with a good clinical response. There are no other cases of the disease in her family.

Case 9 (F III 2)

This male patient was born to a mother of Iraqi origin and a father of Turkish origin (Istanbul), with no consanguinity. As a baby, sucking was noted to be weak, and from the time of birth he had to be spoon fed, his mother literally pouring the milk with a spoon into his mouth. The major abnormality found in infancy was a cleft palate, but bilateral ptosis was also noted. At the age of 9 yrs he underwent palatoplasty, and during that hospitalization a Tensilon test was performed with disappearance of the ptosis. Since then

he has been treated with pyridostigmine and his condition is stable. On examination in our clinic at the age of 17 yrs we found mandibular prognathism, moderate bilateral ptosis with fatigue phenomenon, severe weakness of masticatory muscles, severe weakness of the facial musculature but the orbicularis oculi only mildly affected. All other muscles were normal. On repetitive stimulation of the accessory nerve at a rate of 3 Hz, no decremental response was observed. However, on repetitive stimulation of the facial nerve, recording from the lower lid, a decremental response of 20% was found. Following an injection of Tensilon the decremental response disappeared, to reappear 5 min later. Serum CK was normal, and no AChR antibodies were found in the serum. No other cases of the disease are known in the family.

Case 10 (G III 1)

This male patient was born in Iraq, the product of a consanguinous marriage, the father being the mother's maternal uncle. During the first year of life he had breathing difficulties, attributed to 'polyps'. At the age of 1 yr elongation of the face and of the mandible were noted, unlike any other member of the family. Drooping eyelids were also present at that stage. He did not seek medical attention until the age of 20, when he underwent surgical correction of his mandibular prognathism, mainly for cosmetic reasons. He was referred to our clinic at the age of 40 because of tension headaches. On examination we found an elongated face with a high-arched palate, marked bilateral ptosis with fatigue phenomenon, bilateral weakness of orbicularis oculi, and easy fatigability of speech. A Tensilon test was positive, with marked improvement in ptosis and orbicularis oculi power. On repetitive stimulation of the accessory nerve at a rate of 3 Hz and recording from the trapezius muscle, a decremental response of 13% was observed. After a Tensilon injection the decrement was only 7%. A chest x-ray was normal and serum AChR antibodies were not found. Before he started drug therapy, the patient tried to embark on a political career, but was disabled by the ptosis and the inability to make long speeches. These, along with the other symptoms, improved to a great extent with pyridostigmine treatment.

Case 11 (H III 1)

This male patient, of Iranian origin, was the product of a consanguinous marriage, the father being the mother's maternal uncle. For several weeks after his birth his eyes remained closed, since when he has had severe bilateral ptosis. Another abnormality noted in infancy was an elongated and protruding mandible. His condition remained unchanged until his eighteenth year. Since then he has also noticed mild weakness in his limbs after exertion. At the age of 18 he underwent surgical correction of mandibular prognathism. He was referred for examination in our clinic before a ptosis operation at the age of 24 yrs.

We found severe bilateral ptosis with fatigue phenomenon, marked weakness of masticatory muscles, orbicularis oculi and other facial muscles, and neck flexors. There was also a mild weakness of the deltoid and triceps after prolonged voluntary effort. A Tensilon test was positive, with improvement in ptosis and facial weakness. A chest x-ray was normal and serum AChR antibodies were not detected. EMG was refused by the patient. No other cases of the disease are known in the family. The patient's condition improved and has remained stable with pyridostigmine treatment.

Case 12 (I III 2)

This female patient was born in Iran. The father was the mother's maternal uncle. At the age of 24 yrs she had an operation for extrauterine pregnancy. After the operation respiratory insufficiency developed, which required assisted ventilation. After extubation the patient disclosed that at the age of 7 yrs a diagnosis of myasthenia gravis had been made, and that she used to take small doses of prostigmine until her pregnancy, when she ceased all medication. She also had had rheumatic heart disease, with mitral stenosis and regurgitation. On examination, she had an elongated face, mandibular prognathism and a high-arched palate, ptosis with fatigue phenomenon, weakness of orbicularis oculi and other facial muscles, and nasal speech. A Tensilon test was positive. A chest x-ray showed a normal mediastinum, no serum AChR antibodies were detected. Subsequently she had an open mitral commissurotomy, and during the operation the thymus was excised. Histology showed normal thymic tissue. The patient's condition has been stable with pyridostigmine treatment. She has 2 normal brothers and 2 sisters, 1 of whom is myasthenic (Case 13).

Case 13 (I III 5)

A younger sister of Case 12. She was noted to have poor sucking from birth. On examination at the age of 19 yrs, she had an elongated face, high-arched palate, bilateral ptosis with fatigue phenomenon,

and moderate weakness of orbicularis oculi and other facial muscles. A Tensilon test was positive. Serum AChR antibodies were not present. She improved considerably on pyridostigmine treatment.

Case 14 (J IV 3)

This patient was examined by us at the age of 32 yrs. His parents were second cousins and were born in Iran. Since birth he had bilateral ptosis which increased towards the evening and when he was tired. Otherwise he was asymptomatic and worked full time on a job that required physical exertion. On examination he had an elongated, triangular face, a high-arched palate, mandibular prognathism with an open bite and crowding of the teeth. Bilateral ptosis was present, with a marked fatigue phenomenon. Extraocular movements were normal. The pterygoids, masseters and temporalis muscles were weak and atrophic. The orbicularis oculi and the other facial muscles showed marked weakness. The speech had a nasal quality. The sternocleidomastoids were minimally affected, and all limb muscles were normal. A Tensilon test was positive, and EMG showed a decremental response on stimulation of the accessory nerve at 3 Hz. No AChR antibodies were found. No other cases were known in the family. The patient was given pyridostigmine with improvement in the ptosis.

DISCUSSION

The clinical syndrome of congenital myasthenia was first described by Bowman (1948), and was further elaborated by Levin (1949). Characteristically, symptoms appear at birth or shortly thereafter. Ptosis and ophthalmoplegia are the most prominent manifestations, frequently associated with facial weakness (Fenichel, 1978). Generalized weakness occurs only occasionally, and is usually mild. The disease follows a benign but persistent course without fluctuations (Levin, 1949; Millichap and Dodge, 1960). It is a hereditary disease with frequent occurrence in siblings but absence of myasthenia in the mother (Levin, 1949; Fenichel, 1978). There are no serum AChR antibodies, and immune complexes are absent from the neuromuscular junction (Engel, 1984). Congenital myasthenia is thus distinguished both in the pathogenesis and in the clinical manifestations from the immune mediated transient neonatal myasthenia and juvenile myasthenia gravis, and also from the separate clinical entity of familial infantile myasthenia gravis (FIMG) (Fenichel, 1978; Albers *et al.*, 1984).

In recent years electrophysiological, cytochemical, histological and ultrastructural studies have delineated several distinct syndromes with presynaptic and postsynaptic defects (Swift, 1981; Engel, 1984) such as endplate acetylcholinesterase (AChE) deficiency (Engel *et al.*, 1977), slow channel syndrome (Engel *et al.*, 1982), endplate AChR deficiency (Vincent *et al.*, 1981) and putative defects in the AChR macromolecule (Vincent *et al.*, 1981; Lecky *et al.*, 1986). The 14 patients described here form a distinct and relatively large and homogenous group with unique clinical features.

Facial malformations. All patients have mandibular prognathism with class III malocclusion and open bite. The findings were confirmed by cephalometric x-rays in most cases. Three patients were first seen by a neurologist long after surgical correction of prognathism. These operations were carried out by different surgeons in different hospitals, without any suspicion of an associated neurological abnormality or genetic syndrome. All patients also have a high-arched palate and almost all have an elongated face. These facial skeletal malformations, coupled with bilateral ptosis and limited facial expression, give the patients a characteristic myopathic look. We have not encountered in these families cases of myasthenia without the facial deformities, or vice versa. There seems to be a uniform association between the myasthenia and the facial skeletal abnormalities.

On reviewing the literature we found reference to similar features in only 1 case. Kott and Bornstein (1969) described an Israeli family of Oriental Jewish origin with 4 cases of congenital myasthenia in siblings, 1 of which (their second patient) was scaphocephalic, with marked prognathism and a high palate. The clinical manifestations—distribution of weakness, course of the disease and response to cholinesterase inhibitors—are remarkably similar to our cases. In the 'slow channel' subtype of congenital myasthenia, 2 of the patients were said to have a high-arched palate, but no other facial deformities were noted in the report or in the patients' photographs (Engel *et al.*, 1982). The clinical syndrome is also very different from our cases.

Distribution of weakness (Table 2). All 14 patients had bilateral ptosis and predominant facial muscle weakness. Eleven (79%) had weak masticatory muscles, and 12 (86%) had easy fatiguability on prolonged speech. In 5 patients neck muscles were involved. Very mild limb muscle involvement was present in 3 cases.

TABLE 2 DISTRIBUTION OF WEAKNESS

	No	Percentage
Ptosis	14	100
Facial musculature	14	100
Muscles of mastication	11	79
Speech	12	86
Swallowing	1	7
Neck muscles	5	36
Limb muscles	3	21

This distribution of muscle weakness is compatible with most previous reports of congenital myasthenia, where extraocular and facial muscle involvement have usually predominated (Millichap and Dodge, 1960; Fenichel, 1978). Weakness of the masticatory muscles has been reported inconsistently, but was common and sometimes very prominent in our patients. Our patients are also remarkable for the restriction of extraocular muscle weakness to ptosis, and the absence of ophthalmoplegia (except for diplopia on repeated saccades in Case 1). Such restricted extraocular muscle involvement has occasionally been reported (Vincent *et al.*, 1981; Lecky *et al.*, 1986). It should also be noted that 2 patients (Cases 7, 8) suffered recurrent severe respiratory infections in the first year of life, usually described in familial infantile myasthenia gravis (FIMG) and not in congenital myasthenia. However, beyond infancy these patients had ptosis and weakness of facial and masticatory muscles indistinguishable from the rest of our patients.

Natural history. In our patients the disease had an early onset, mild severity and stable course, with hardly any progression and also no spontaneous remission over the years. This is characteristic of congenital myasthenia (Fenichel, 1978). We find it remarkable that despite the very early onset of symptoms, diagnosis was often delayed, and half of the patients were diagnosed between the ages of 18 and 42 yrs. The skeletal facial anomaly was often the chief complaint. Delayed diagnosis of congenital myasthenia has been noted before (Walsh and Hoyt, 1959; Fenichel, 1978; Smit and Barth, 1980).

Electromyographic findings. A decremental response on repetitive stimulation of either

the accessory or the facial nerve at a rate of 3 Hz was usually demonstrable, but was not invariable. In no patient was a repetitive compound muscle action potential activity evoked by single nerve stimuli. Myopathic changes in the EMG were not seen.

Absence of antibodies to AChR. Although AChR antibody determination may seem superfluous in patients with congenital hereditary myasthenia, several authors have emphasized the importance of this test in avoiding confusion with transient neonatal myasthenia in the neonatal period, and with juvenile myasthenia gravis after the age of 1 yr (Vincent and Newsom-Davis, 1979; Seybold and Lindstrom, 1981).

Response to cholinesterase inhibitors. All patients had an unequivocally positive Tensilon test, and showed clinical improvement with pyridostigmine. This is typical of only some of the congenital myasthenic syndromes reported in the literature, depending on the underlying abnormality in neuromuscular transmission (Engel, 1984). As could be expected, the 2 patients who underwent thymectomy did not benefit from the procedure.

Ethnic clustering. All 14 patients are of Oriental Jewish extraction of either Iraqi or Iranian origin. Five of the families originated in Iraq and 5 in Iran. An attempt to trace the roots of these families to one geographical region was not successful. Historically, close ties existed between Iraqi and Iranian Jewry in former times and it is known that these two Jewish communities also share other genetic diseases (Goodman, 1979). Congenital myasthenia has been reported in many parts of the world: USA, England, Switzerland, France, the Netherlands, Norway, Israel, India and Japan amongst others (Namba *et al.*, 1971). Most reports have consisted of single families, and never before has a distinct congenital myasthenic syndrome been associated with any definite ethnic group.

The single family reported initially by Bornstein (1953) and later by Kott and Bornstein (1969) was Oriental Jewish; the exact country of origin was not specified. As stated above, this family may have had the same syndrome that we are describing here. Also of interest is a case reported by Lecky *et al.* (1986), of an Iraqi woman (probably non-Jewish) with congenital myasthenia. The clinical neurological manifestations and the mode of inheritance somewhat resembled our cases, but no facial deformities were mentioned. The same group also reported the case of an Iranian man (not said to be Jewish) with 'myasthenic myopathy', most probably hereditary, but the clinical syndrome was very different from ours and no facial deformities were noted (Morgan-Hughes *et al.*, 1981).

Inheritance. In 7 of 10 families there was close parental consanguinity. Marriage between first cousins occurred in 4 families, and between uncle and niece in 3. In no case was there vertical transmission from parent to offspring. In 7 families there were only single cases of the disorder. Two families had 2 cases each (in siblings), and 1 family had 4 cases in two successive generations. The mode of inheritance in these families is obviously autosomal recessive. No clinical abnormalities were noted to be present in the heterozygous unaffected parents. Autosomal recessive inheritance in congenital myasthenia was first suggested by Levin (1949) and later by others (Bundey, 1972; Namba *et al.*, 1971; Seybold and Lindstrom, 1981). Some congenital myasthenic syndromes also seem to be transmitted by autosomal dominant genes (Engel *et al.*, 1981). In most of the families described in the literature only one generation was affected. Two affected generations in the same family have been reported (Warrier and Pillai, 1967) infrequently.

The relationship between myasthenia and facial deformities

A pertinent question is whether the facial malformations described above constitute developmental abnormalities secondary to the neuromuscular defects or primary malformations caused by the same genetic defect. An authoritative textbook of orthodontics (Begg and Kesling, 1977) states that 'for proper development of the dental arches and for proper development of tooth occlusion there is, no doubt, during the various functions of the dental apparatus a proper balance between the muscular forces exerted by the lips and cheeks external to the dental arches, and the muscular forces exerted by the tongue, internal to the dental arches. It appears that besides the muscles of the lips, cheeks, face and tongue, the muscles of mastication and deglutition exert forces on the jaws and teeth, so that the function of no part of the dento-maxillo-facial complex is independent of and unaffected in its development by the function of the other parts. According to Graber (1972), malocclusions may involve four tissue systems: teeth, bones, muscles and nerves. Any disharmonious relationship between teeth and jaws or abnormal function of muscles and nerves in the dentofacial complex could result in malocclusion.

The interplay between muscular traction and skeletal structure has also interested investigators of the recurrence of mandibular prognathism after corrective surgery (Moss, 1985). The possible relationship between a transient neuromuscular disease of infancy and the development of mandibular prognathism has also been hypothesized (Fraudet, 1978). Aetiological factors involved in prognathism and malocclusions are not well understood. Genetic factors probably play an important role and mandibular prognathism in man has been reported to be inherited in three different ways: as an autosomal dominant trait with variable penetrance, a simple recessive trait, and a polygenic trait with a threshold for expression (Huang *et al.*, 1981). A wide range of environmental factors have also been suggested as contributory to the development of mandibular prognathism (Litton *et al.*, 1970).

A point in favour of the hypothesis that the facial deformities in our patients are secondary to the neuromuscular defect is the occurrence of a long and narrow face, high-arched palate and dental malocclusion in a few congenital myopathies that involve the facial musculature (Engel and Banker, 1986). Abnormal development of the involved muscles in utero causes changes in traction forces applied to the developing bones, which may result in skeletal anomalies. On the other hand, many cases of congenital myasthenia have been reported with the typical prominent facial weakness but without any associated changes in skeletal features. Many patients' photographs have been published and prove that facial skeletal deformities were indeed absent from all these cases. In a case of congenital myasthenia with arthrogryposis (Smit *et al.*, 1980, 1987), severe skeletal abnormalities were observed, but no facial malformations were reported. In another case associated with arthrogryposis (Hageman *et al.*, 1986) micrognathia was mentioned. The weakness of the muscles of mastication, so common in our patients, may be of importance in the pathogenesis of the facial anomalies.

In conclusion, we postulate that an elongated face, a high-arched palate and mandibular prognathism with malocclusion are secondary features of our syndrome where the primary defect is neuromuscular. The true prevalence of this syndrome among prognathic patients with malocclusion may be higher than hitherto suspected. A prospective study of patients in prognathism clinics is planned in order to answer this question.

Nature of the neuromuscular transmission defect

More detailed studies are warranted to elucidate the underlying defect in neuromuscular transmission. Comparing our clinical, genetic and electromyographic data with those reported in the more fully investigated congenital myasthenic syndromes (Table 3) we can infer the following.

Our results are not compatible with the syndrome of putative defect in ACh resynthesis or packaging reported by Hart *et al.* (1979), which clinically resembles FIMG and does not predominantly involve facial or masticatory muscles. The syndrome described by Albers *et al.* (1984) and attributed to abnormal ACh resynthesis, mobilization or storage, also clinically resembles FIMG and is in addition resistant to anticholinesterase medication. In the syndrome of endplate AChE deficiency (Engel *et al.*, 1977) generalized weakness is reported, the electrodiagnostic examination shows a repetitive compound muscle action potential response to a single nerve stimulus, and cholinesterase inhibitors are ineffective. In the slow channel syndrome there is selective weakness of cervical, scapular and dorsal forearm muscles, the inheritance is autosomal dominant, the Tensilon test is negative and a single nerve stimulus results in a repetitive compound muscle action potential (Engel *et al.*, 1982; Oosterhuis *et al.*, 1987). Repetitive motor responses to single nerve stimuli also characterize the congenital myasthenic syndrome with increased numbers of ACh receptors (Cornblath *et al.*, 1985). The syndrome of congenital endplate AChR deficiency is a heterogeneous group that includes a number of incompletely defined syndromes. In the patients described by Vincent *et al.* (1981) neonatal hypotonia, ptosis and ophthalmoplegia were followed by progressive facial and generalized weakness, a clinical course substantially different from that observed in our patients. The mode of inheritance, electromyographic findings and response to cholinesterase inhibitors, however, are in agreement with our results. In the patient studied by Morgan-Hughes *et al.* (1981) with presumed abnormality of the AChR macromolecule, the distribution of weakness and clinical course differ from our patients, and the Tensilon test results in either no or only a slight and partial response. Finally, the Iraqi patient described by Lecky *et al.* (1986) with a suggested abnormality of the AChR macromolecule causing negligible alpha bungarotoxin binding had clinical features which may resemble our patients, and was also responsive to cholinesterase inhibitors.

It would be premature to suggest the nature of the underlying defect in neuromuscular transmission in our patients on the basis of the data presented here, but some postsynaptic defect of the AChR macromolecule may seem most plausible. Many hitherto unknown genetically determined abnormalities of AChR, cytoskeletal proteins, synaptic vesicles, presynaptic membrane or junctional folds may theoretically be conceived (Engel, 1980). Electrophysiological, cytochemical, light microscopical and ultrastructural studies of intercostal muscle biopsies from our patients are being planned and may lead to a better understanding of this new syndrome.

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MYELOPATHY ASSOCIATED WITH HUMAN T CELL LYMPHOTROPIC VIRUS TYPE I (HTLV-I) IN NATAL, SOUTH AFRICA

A CLINICAL AND INVESTIGATIVE STUDY IN 24 PATIENTS

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SUMMARY

Unexplained spastic myelopathy in black (Zulu) patients, similar to that seen in the tropics, has previously been described from Natal, South Africa. Following reports linking the human T cell lymphotropic virus type I (HTLV-I) to spastic myelopathy, we undertook a prospective and retrospective search for HTLV-I antibodies in 36 patients who were labelled as having unexplained myelopathy; 24 (66%) were positive and HTLV-I was isolated from 4 out of the 6 patients whose peripheral blood lymphocytes were cultured. Eighteen (75%) gave a short history (less than 6 months). There was a female preponderance (71%), spinothalamic dysfunction was common (55%) and as many as half were severely disabled (50% wheelchair bound). Routine laboratory studies showed no specific trends apart from hypergammaglobulinaemia and CSF pleocytosis (greater than 5 cells/ μ l in 66% of patients). The total CSF protein was raised (greater than 0.4 g/l) in 45% of patients. The IgG index was greater than 0.7 in 15 of 19 patients. Conventional myelography did not show any specific abnormalities. Computer assisted myelography was undertaken in 22 patients; 3 showed arachnoiditis and 2 spinal cord atrophy. Periventricular lucencies were seen in 1 of 10 patients who had computed tomography of the head. Nerve conduction studies demonstrated abnormalities in 46% of the patients indicating that subclinical peripheral nerve dysfunction was common. Visual evoked responses were abnormal in only 1 patient but brainstem auditory evoked response studies showed some abnormality in 42% of the patients. The finding of HTLV-I antibodies in a significant number, and the isolation of HTLV-I from the blood in 6 of our black patients with noncompressive myelopathy, represents a substantial clinical advance. Future studies should define more clearly the role of the virus in this disorder.

INTRODUCTION

Spastic paraparesis without evidence of spinal cord compression has been described from various tropical and subtropical areas including Jamaica (Montgomery *et al.*, 1964), Colombia (Román *et al.*, 1985), Seychelles (Kelly and De Mol, 1982), South India (Mani *et al.*, 1969) and South Africa (Cosnett, 1965). It represents a major cause of neurological disability in these countries. For example, Kelly and De Mol (1982) found a prevalence ratio of 127 per 100 000 of the population in the Seychelles and in a series of 330

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paraplegic patients in Natal, Wallace and Cosnett (1983) found unexplained myelopathy to be the most common diagnostic category after trauma and vertebral tuberculosis.

The clinical features described from different parts of the world have been similar (Román, 1988). There is a subacute or gradual onset of increasing spasticity and weakness of the legs, frequent sphincter dysfunction and mild or insignificant sensory disturbance. Brisk tendon reflexes in the upper limbs are seen in about half the patients. Mental function and examination of the cranial nerves are usually normal.

Apart from epidemics of cassava-related myelopathy in Mozambique (Casadei *et al.*, 1984) and lathyrism in India (Prasad and Sharan, 1979) the aetiology of the spastic myelopathy had remained elusive until 1985. The 'serendipitous' finding of HTLV-I antibodies in 2 patients with tropical spastic paraparesis (TSP) by Gessain *et al.* (1985) led to several other studies confirming the association. Rodgers-Johnson *et al.* (1988) found HTLV-I antibodies in 82% of 47 Jamaicans with TSP. In the Seychelles, Román *et al.* (1987) found HTLV-I antibodies in 17 (85%) of 20 serum samples from patients with TSP. The Colombian experience was similar, with 52 of 55 (94%) patients testing positive (Zaninovic *et al.*, 1988). Newton *et al.* (1987) tested 11 West Indian born UK residents with unexplained myelopathy and all were positive. These patients had been in the UK for a mean of 26 yrs. Exposures to the virus probably took place while the patients were still in the West Indies.

Cases have also emerged from beyond the tropics. Osame *et al.* (1987) described 6 patients from Japan with chronic progressive myelopathy who had high antibody titres in the serum and CSF. Two of the patients reported by Bhagavati *et al.* (1988) were born and resident in the USA.

Seroepidemiological studies in Africa have confirmed the presence of the virus with positivity ranging from 0.6% in Morocco to 16.9% in northwest Tanzania (de-Thé *et al.* (1985). An incidence of up to 3.5% was reported in South Africa (Becker *et al.*, 1985; Botha *et al.*, 1985). Reports of HTLV-I antibodies in patients with TSP in Africa, however, have been scanty (Gessain *et al.*, 1986, 1988). Between September 1987 and June 1988 we tested prospectively all patients with the initial diagnosis of unexplained myelopathy for HTLV-I antibodies. Retrospective analysis was performed on serum and CSF from previous patients with this diagnosis. A total of 36 (15 prospective, 21 retrospective) patients with unexplained myelopathy was identified. Of these, 24 (10 prospective, 14 retrospective) were positive for HTLV-I antibodies. We report on the clinical, laboratory, electrophysiological and radiological findings in these 24 patients.

METHODS

Patients

All patients with an initial diagnosis of unexplained myelopathy admitted between September 1987 and June 1988 were assessed prospectively. Retrospective analysis was undertaken on those patients with this diagnosis who had serum and/or cerebrospinal fluid (CSF) available for testing for HTLV-I antibodies.

Control group

The control subjects were derived from patients with other neurological diseases, patients admitted for plastic surgery and trauma cases admitted to orthopaedic wards.

Laboratory investigations

The following investigations were performed in all patients: haemoglobin concentration, white cell count, erythrocyte sedimentation rate (ESR), serum immunoglobulins, serological tests for syphilis, antinuclear factor, one or more tests for schistosomiasis (serum immunohaemagglutination, urine and stool examination and rectal mucosal biopsy). CSF was taken for cell count, protein, globulin, glucose, bacterial culture and serological tests for syphilis. The IgG index, as a measure of the intrathecal production of immunoglobulins, was calculated in some of the patients. Tests for the following were performed in some of the patients: antibodies to the Epstein-Barr (EBV), Herpes simplex and the Varicella-zoster viruses and to *Mycoplasma pneumoniae*, the hepatitis B antigen and antibody, serum folate and vitamin B12 concentrations and cryptococcal antigen in the CSF.

Virological studies

Specimens of blood and CSF were tested for the presence of antibodies to HTLV-I using an enzyme-linked immunosorbent assay. All positive specimens were subsequently confirmed by Western blotting (Dupont HTLV-I ELISA and Dupont HTLV-I Western Blot, Biotech Research Laboratory, Rockville, MD, USA). All blood specimens were also screened for the presence of antibodies to human immunodeficiency virus (HIV) by ELISA and any positive results were confirmed by Western blotting (Abbott Recombinant HIV I EIA, Abbott Diagnostic Products, Wiesbaden-Delkenheim, West Germany, and HIV I Western Blot IgG Assay, Diagnostic Biotechnology, Singapore).

Virus isolation was attempted from 6 of the HTLV-I seropositive patients using methods previously described (Becker *et al.*, 1988). Peripheral blood lymphocyte (PBL) cultures were established from heparinized venous blood. The criteria used to determine HTLV-I infection were (1) the establishment of a continuous long-term cell line with the morphology of lymphocytes transformed by HTLV-I infection; (2) the demonstration of the characteristic morphogenesis of HTLV-I particles by electron microscopy of ultrathin sections of these cells, and (3) specific hybridization of DNA extracted from these cells with the reference HTLV-I DNA probe kindly provided by R. Gallo.

Radiological studies

All patients had chest and spinal radiographs. All underwent conventional myelography. Computer assisted myelograms (GE 9 800) were undertaken in 22 patients and 10 patients had CT scans of the head.

Electrophysiological studies

Motor and sensory nerve conduction studies were performed using standard techniques in 15 patients. A minimum of 1 motor and 1 sensory nerve each in upper and lower limbs was evaluated. Full-field pattern reversal visual evoked potentials (VEPs) were recorded in 10 patients and 12 patients underwent brainstem auditory evoked potential (BAEP) testing. All studies were undertaken with a Disa Neuromatic 2000 machine.

RESULTS

Control group

There were 80 patients with other neurological diseases and 14 patients with cosmetic or traumatic disorders.

Clinical data

Out of 36 patients, 24 (66%) with otherwise unexplained myelopathy were positive for HTLV-I antibody; 13 came from rural districts and 11 resided in urban or periurban areas. The age at onset and sex distribution are given in fig. 1. Eighteen patients gave a history of illness of less than 6 months duration, whereas only 2 gave a history of more than 2 yrs. The main symptoms and signs are summarized in Tables 1 and 2. No patient complained of headache, or of visual, auditory or bulbar dysfunction.

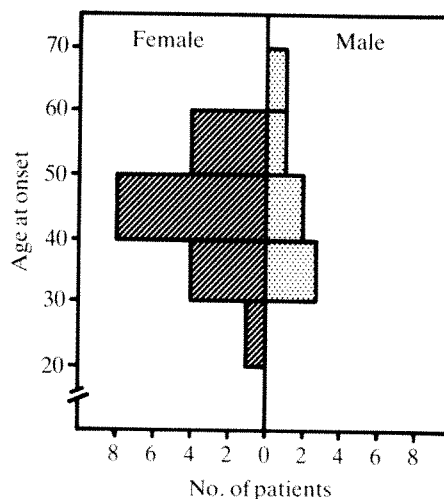


FIG. 1. Distribution of patients according to age at onset and sex.

Viral studies

There were 24 patients (66%) who were positive for HTLV-I antibodies. On Western blot testing all showed the same strong specific multiple banding pattern indicative of well established infection (fig. 2). Of the 20 CSF specimens examined, 18 (90%) from these seropositive patients were confirmed as being positive for antibodies to HTLV-I, with similar but weaker banding patterns than those found in the corresponding sera. The CSF specimens of the remaining 2 patients (Cases 11 and 13) were strongly positive for antibodies to the p24 gag protein only (fig. 3). No subject in the control group was positive for antibodies to HTLV-I. All patients were negative for antibodies to HIV-I. The peripheral blood lymphocyte cultures from 3 of the 6 patients for whom virus culture was attempted were shown to be HTLV-I positive within 7 wks of culture (Cases 1, 2, and 6) whereas a fourth was found positive after 3 months (Case 3).

Other laboratory investigations

Anaemia was present in 9/17 (53%) females (haemoglobin less than 12 g/dl) and in 6/7 (86%) males (haemoglobin less than 14 g/dl); 16 patients had an ESR of more than 20 mm/h (Westergren). Four patients had a total white cell count of less than

TABLE 1. SUMMARY OF SYMPTOMS AT THE TIME OF PRESENTATION

Symptom	Number	Percentage
Weakness of legs	24	100
Stiffness of legs	24	100
Parasthesiae	11	45
Numbness	13	53
Thoracic or lumbar backache	12	49
Urinary bladder dysfunction	19	78
Faecal incontinence	7	29
Constipation	17	71

TABLE 2. SUMMARY OF NEUROLOGICAL FINDINGS

<i>Neurological finding</i>	<i>Number</i>	<i>Percentage</i>
Lower limbs		
Spasticity	24	100
Weakness	24	100
Brisk knee tendon reflexes	23	94
Brisk ankle tendon reflexes	16	66
Upper limbs		
Weakness	10	41
Increased tendon reflexes	20	82
Abdominal reflexes (recorded in 19 cases)		
Absent	18	95
Plantar responses		
Extensor	19	78
Equivocal	4	16
Flexor	1	4
Degree of motor disability		
Ambulatory without assistance	2	8
Ambulatory with walker or stick	10	41
Wheelchair bound	12	50
Sensory disturbance, lower limbs		
Impaired pin prick and touch	13	53
Impaired proprioception	8	33
Diminished vibration sense	4	16
Approximate sensory level		
None	11	45
Lumbar	2	8
Lower thoracic (T9-12)	5	21
Mid thoracic (T5-8)	3	12
Upper thoracic (T1-4)	2	8
Peripheral loss	1	4

$4.8 \times 10^9/\text{dl}$. Lymphocytosis was present in 4 and eosinophilia in another 4 patients.

A polyclonal gammopathy was demonstrated in 16 patients (66%). Immunoglobulin (Ig) levels were measured in 20 patients. IgG was elevated in 14 (70%), IgM in 15 (75%) and IgA in 7 (35%).

The rapid plasma reagin (RPR) test for syphilis was positive in the serum in 5 patients (20.5%). In all, however, the titre was less than 1:8. The *Treponema pallidum* haemagglutination (TPHA) test was positive in 4 of the 5 patients with positive RPR test.

The serum schistosomal haemagglutination test was performed in 18 patients. This test was negative in 13, weakly positive in 4 (titre less than 1:32) and strongly positive in 1 (1:2048). The strongly positive test was found in a patient who had bilharzial ova on rectal snip. Her bilharzial ELISA test in the CSF, however, was negative.

The CSF findings are shown in Table 3. Bacterial culture (including *M. tuberculosis*) of the CSF was negative in all samples. No patient had a positive CSF fluorescent treponemal antibody test. Tests for ANF and cryptococcal antigen were negative in all patients in whom the test was performed.

Radiological investigations

The chest radiographs were normal in all except 2 which showed nonspecific infective changes. Myelography was normal in all except 2 patients who showed lumbar disc

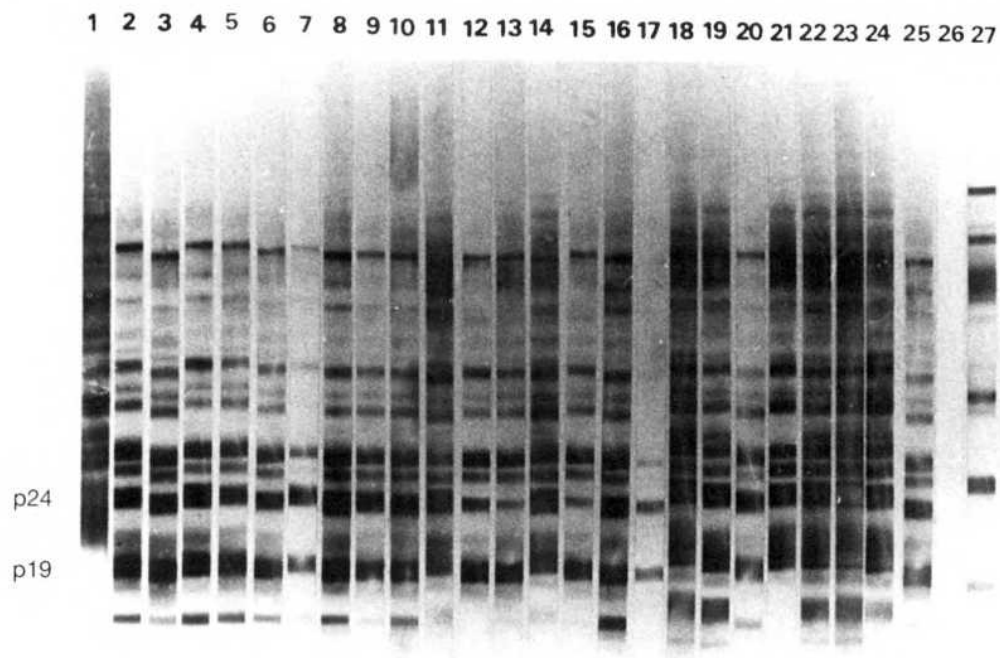


FIG. 2. Western blots for antibodies to HTLV-I in the serum. Lanes 1–24: sera of Cases 1–24, respectively. Lane 25: HTLV-I positive control serum. Lane 26: HIV-I blot using HTLV-positive serum. Lane 27: HIV-I blot using HIV-I positive serum.

annular protrusion and 1 who had minor spondylotic changes in the cervical region. CT myelography was normal in 14, showing annular lumbar disc protrusion in 2, arachnoiditis in 3 (fig. 4), spinal cord atrophy in 2 (fig. 5) and was technically unsatisfactory in 1. Computed tomography of the head was normal in 3, showed minor degrees of atrophy in 5, basal ganglia calcification in 1 and periventricular lucencies in 1 patient. There was no abnormal contrast enhancement in this patient.

Electrophysiological studies

Median sensory and motor nerve conduction studies were performed in 15 patients. Median nerve sensory latency was prolonged in 1 patient (greater than 2.99 ms; stimulus to onset) and the velocity was decreased in 2 patients (less than $36.3 \text{ m} \cdot \text{s}^{-1}$). Median sensory action potential amplitude was normal in all patients (greater than $8.58 \mu\text{V}$). The median distal motor latency was prolonged in 4 patients (greater than 4.38 ms) but the forearm velocity was normal in all. Median evoked muscle action potential amplitude was reduced in 2 patients (less than 7.0 mV) and the F latency prolonged in 1 (greater than 32.7 ms). Sural and common peroneal nerve conduction studies performed in 13 patients are summarized in Tables 4 and 5.

VEPs were obtained in 10 patients. The latency of the P100 component was normal for all of the right eyes but was prolonged for 1 left eye (114 ms; normal less than

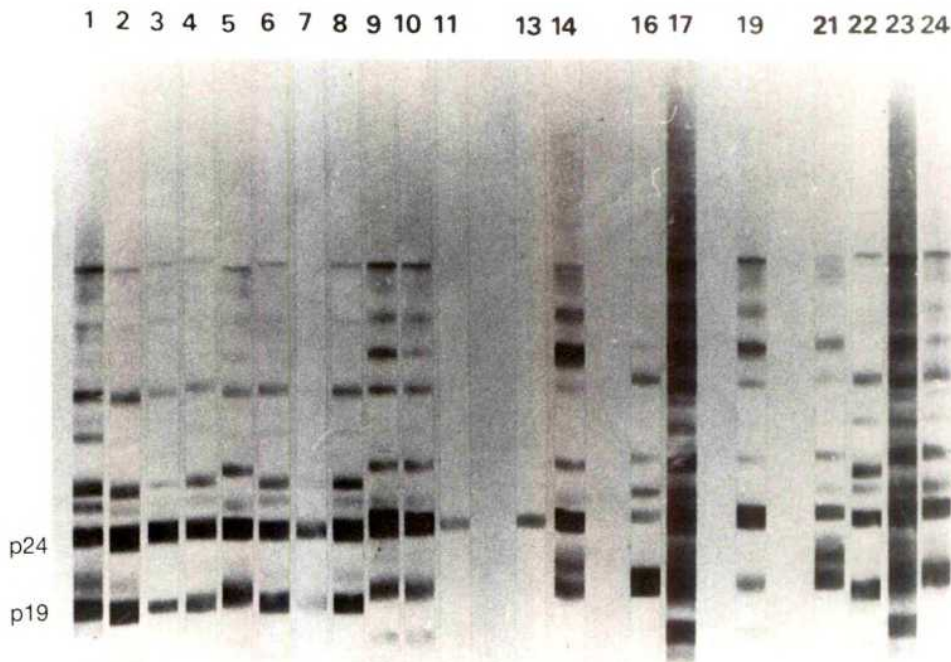


FIG. 3. Western blots for antibodies to HTLV-I in CSF. Samples from Cases 12, 15, 18 and 20 are missing.

110 ms). BAEPs were recorded in 12 patients. The results are summarized in Table 6. Abnormality was noted in 42% of the patients, especially involving the later components.

DISCUSSION

Geographical, clinical and seroepidemiological background

Natal is the smallest province of the Republic of South Africa and lies between latitudes 27–31° S and longitudes 29–33° E (fig. 6). It is bordered on the east by the Indian Ocean while the Drakensberg mountains form the Western boundary. Natal, within which is the homeland of Kwa Zulu, is the home of 4.56 million Zulus (South African Statistics, 1986).

The neurology unit at Wentworth Hospital in Durban is the only specialist referral centre for the area. Between January 1985 and June 1988 a total of 1388 black patients was admitted. Of these, 371 (26.8%) had myelopathies of various causes. Analysis of the frequency of various types of myelopathy in black patients would be inaccurate as most patients with vertebral disease (e.g., tuberculosis) are referred directly to orthopaedic surgeons and cases of spinal tumour are sent to neurosurgeons. However, we believe that nearly all cases of undiagnosed myelopathy would at some stage in their illness be referred to us.

TABLE 3. DETAILS OF CSF FINDINGS

Case	Poly- morphs (cells/ μ l)	Lympho- cytes (cells/ μ l)	Protein (g/l)	Globulin	Glucose (mmol/l)	IgG Index
1	6	12	0.80	T	2.50	ND
2	8	68	0.74	+	1.90	0.84
3	14	2	0.88	+	2.10	1.59
4	16	8	0.44	+	2.80	1.46
5	0	48	0.56	T	2.70	0.04
6	0	0	0.80	+	2.30	0.07
7	0	0	0.18	0	2.00	0.80
8	28	8	0.74	T	2.70	ND
9	2	32	0.30	T	2.40	ND
10	4	2	0.18	0	2.70	2.24
11	0	0	0.20	T	2.40	0.43
12	0	6	0.20	0	2.90	ND
13	0	8	0.44	0	2.80	0.53
14	4	8	0.32	0	2.10	1.48
15	2	9	0.40	0	3.30	1.28
16	0	0	0.27	0	2.80	0.88
17	40	2	0.70	+	2.20	3.60
18	0	0	0.16	0	2.50	0.97
19	0	8	0.40	T	3.20	1.27
20	0	0	0.24	T	2.40	ND
21	2	34	0.42	0	2.20	15.9
22	0	0	0.33	T	2.30	4.4
23	6	8	0.56	+	2.50	1.39
24	0	4	0.20	0	2.90	2.92

ND = not done. IgG Index: normal <0.7. T = trace.

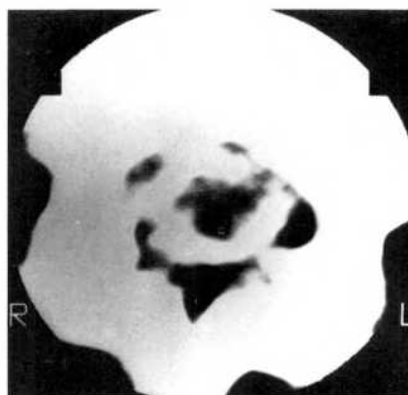


FIG. 4. CT myelography demonstrating arachnoiditis of the midthoracic cord.

Clinical features

The mean age of our patients was 46.2 yrs whereas many of Cosnett's (1965) patients were below 25 yrs of age. Our youngest patient was 27 yrs old at the onset of her illness.

Cosnett (1965) noted a male preponderance of 2:1 in unexplained myelopathy. This was in keeping with earlier studies elsewhere (Montgomery *et al.*, 1964; Kelly and De Mol, 1982; Román *et al.*, 1985). In more recent studies, however, where patients have

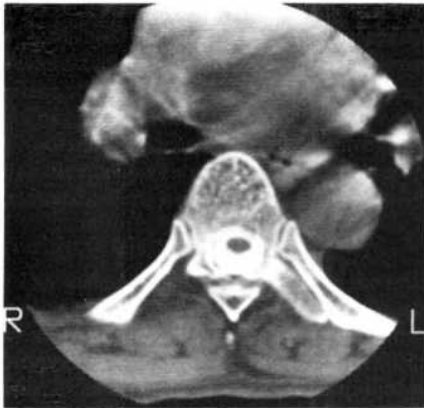


FIG. 5. CT myelography showing atrophy of the midthoracic cord.

TABLE 4. SURAL NERVE CONDUCTION STUDIES IN 13 PATIENTS*

Case	Latency (ms)	Amplitude (μV)
1	4.10	3.40
3	2.6	7.20
5	3.6	1.20
6	4.4	6.40
9	3.4	8.2
10	NR	NR
11	3.2	5.6
12	2.5	16.0
13	1.8	16.8
14	NR	NR
16	2.9	17.0
21	3.2	3.0
22	4.0	2.6
Normal	< 3.4	> 5.0

* All studies orthodromic except in Cases 12, 13 and 16. NR = no response.

TABLE 5. COMMON PERONEAL MOTOR NERVE CONDUCTION STUDIES

Case	DML (ms)	Amplitude (mV)	Conduction ($m \cdot s^{-1}$) velocity
1	5.0	1.12	36.4
3	5.6	0.48	37.5
5	4.2	7.00	50.0
6	4.4	0.71	41.6
9	4.6	3.50	36.4
10	4.2	4.40	43.1
11	3.6	15.20	25.5
12	4.6	NA	43.1
13	3.9	4.80	56.4
14	4.0	0.80	45.9
16	3.8	21.00	47.4
21	4.0	1.01	53.5
22	3.5	3.36	35.0
Normal	< 5.1	> 4.17	> 41.0

DML = distal motor latency; NA = not available.

TABLE 6 SUMMARY OF BAEP RESULTS

	<i>Number of abnormal latencies</i>							
	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	<i>V</i>	<i>I-III</i>	<i>III-V</i>	<i>I-V</i>
Right	0	1	1	3	5	4	2	5
Left	0	0	0	3	4	2	1	2

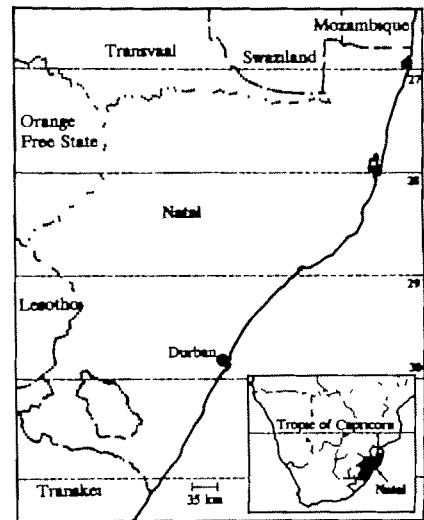


FIG. 6. Map of Natal. Inset shows Southern Africa, with Natal south of the Tropic of Capricorn.

been shown to be HTLV-I positive, a female preponderance of between 57 and 90% has been found (Rodgers-Johnson *et al.*, 1988); 71% of our patients were female. The reason for the female preponderance is unclear. It may be an artefact of referral but it is noteworthy that HTLV-I transmission from husband to wife is 60.8% and from wife to husband 0.4% (Kajiyama *et al.*, 1986).

The mode of onset, duration of illness, the symptomatology and findings on examination in the present series were similar to those previously described in Natal (Cosnett, 1965). Unlike the typical TSP (Román, 1988), but similar to the Japanese study (Osame *et al.*, 1987) spinothalamic dysfunction was seen in 10 patients (44.6%). Half the patients in our study were wheelchair bound whereas other studies have indicated that most patients remain ambulatory with or without aids (Rodgers-Johnson *et al.*, 1988; Zaninovic *et al.*, 1988). The course of the disease is therefore more rapid and aggressive in our patients. The reason for this is unclear but may be due to a high viral load (*see below*).

Clinical peripheral nerve dysfunction was seen in 4 patients (16%). In 1 patient ankle tendon reflexes were depressed, in 2 they were lost and in 1 there was a 'stocking' sensory loss. Peripheral nerve disturbance has not been documented in other large clinical studies (Rodgers-Johnson *et al.*, 1988; Román, 1988), although Zaninovic *et al.* (1988) mentioned that ankle jerks may decrease or disappear in the evolution of the disease. More recently, Said *et al.* (1988) described histological changes in a peripheral nerve of a patient with HTLV-I myelopathy but he had questionable clinical deficit. We are

presently evaluating the sural nerve biopsies from 6 patients who had both clinical and electrophysiological evidence of peripheral nerve dysfunction.

Laboratory studies

The routine laboratory studies did not demonstrate specific trends. Not surprisingly hypergammaglobulinaemia was a frequent finding (66%). Mild normocytic normochromic anaemia was commonly seen and the ESR was raised in two-thirds of the patients.

The RPR test for syphilis was positive in low titres (less than 1:8) in 5 patients (20.5%); 4 of these had a positive TPHA. None of our patients had a positive CSF FTA-ABS test. These findings differ from Jamaican patients who have demonstrated positivity rates of 46 and 4% in serum and CSF, respectively (Rodgers-Johnson *et al.*, 1988). Similar high positivity rates were obtained in Colombia (Zaninovic *et al.*, 1988). Vernant *et al.* (1987), however, found figures comparable with ours in Martinique. Osame *et al.*, (1987) did not comment on syphilitic serology in their Japanese patients. The high frequency of treponemal antibodies in some of the studies remains unexplained.

CSF pleocytosis (greater than 5 cells/ μ l) was seen in 16 patients (66%) while the total protein was raised (greater than 0.4 g/l) in 45% of the patients. These findings differ from the typical TSP cases but resemble the Japanese patients (Osame *et al.*, 1987). A possible explanation may be that many of our patients presented early, and therefore in the active stage of their disease. An unexpected finding was a low CSF glucose (less than 2.20 mmol/l) in 5 patients. The IgG Index was elevated in 15 of 19 patients, suggesting intrathecal synthesis of immunoglobulins.

Virological findings

The presence of multiple bands in addition to p19 and p24 in both serum and CSF was indicative of well established infection. Furthermore, the early establishment within 7 wks of a productively infected lymphocyte cell line in 3 of the 6 cultures suggested a high viral load. These findings are highly significant when seen against a background of a seroprevalence of 3.5% in South Africa.

Radiological findings

Conventional iopamidol myelography did not show specific abnormality. However, CT-myelography in 21 patients showed arachnoiditis in 3 and spinal cord atrophy in 2 patients. The arachnoiditis would be consistent with findings of patchy adhesions of the cord to dura seen at necropsy (Liberski *et al.*, 1988). Cord swelling on CT myelography has been described in 1 patient (Johnson *et al.*, 1988) but none of our cases demonstrated this abnormality. CT myelography thus provides some information of the pathology during life. It is probable that magnetic resonance imaging (MRI) of the cord will be more informative.

Scattered periventricular lesions have been demonstrated on MRI of the brain (Newton *et al.*, 1987), indicating that the HTLV-I produces a more widespread disease than the clinical myelopathy suggests. We do not have easy access to MRI facilities. Computed tomography of the brain was undertaken in 10 patients. Only 1 showed features similar to that seen on MRI.

Electrophysiological studies

Evidence of peripheral nerve dysfunction (motor and/or sensory) was present in approximately half of the patients indicating that subclinical involvement, though mild, was common. Of 19 patients described from Seychelles by Ludolph *et al.* (1988), 8 had abnormalities of sural conduction studies and 11 had some abnormality of peroneal nerve function. Barkhaus and Morgan (1988) found abnormalities in a smaller proportion of Jamaicans with spastic paraparesis. Apart from a case report showing an inflammatory neuropathy (Said *et al.*, 1988), the basis for the peripheral nerve abnormalities remains unexplained. None of our patients was debilitated or had other systemic illness and most had a short history of illness. Repeated trauma and compression seemed unlikely causes. Peripheral nerve dysfunction has been described with the human immunodeficiency virus (HIV), a retrovirus (Dalakas and Pezeshkpour, 1988). It is probable that similar pathogenic mechanisms occur in the peripheral neuropathy of HTLV-I infection.

CONCLUSION

The finding of HTLV-I antibodies in a significant number of the patients and the isolation of the virus in 4 patients represents a major advance in the understanding of otherwise unexplained myelopathy in Natal. Like the Japanese (Kakigi *et al.*, 1988), we found that VEP abnormalities were rare. This is in contrast to the findings of Newton *et al.* (1987) who found abnormalities in 8 of the 12 patients of West Indian origin in the UK. The reason for this finding is unclear. However, BAEPs were abnormal in 41% of our patients, again confirming the widespread nature of the disorder.

That an association between the virus and myelopathy exists is clear, but the underlying pathogenic mechanisms remain to be defined. Host factors need to be considered and the role of other infections should be evaluated. Thus we are currently evaluating the association between HTLV-I infection and EBV activity. Culture of neural tissue or *in situ* hybridization studies have to be done to confirm or refute direct HTLV-I infection. We also need to explain the HTLV-I antibody negative myelopathy patients. Some of these patients may yet have HTLV-I infection and attempts at antigen and DNA detection should be undertaken (*see* Bhagavati *et al.*, 1988). At a broader level, community based studies are required to trace contacts of patients and devise strategies for health education.

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ADDENDUM

Since preparing this paper we have collected a further 20 patients with HTLV-1 associated myelopathy. Their clinical and laboratory profiles are similar to the earlier patients, again emphasizing an aggressive course. It is noteworthy that only 2 of the 21 patients recently described by Cruickshank *et al.* (1989) could walk unaided. This finding, which differs from other reports, needs further elucidation.

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HETEROGENEITY IN PROGRESSIVE APHASIA DUE TO FOCAL CORTICAL ATROPHY

A CLINICAL AND PET STUDY

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SUMMARY

Six patients with a slowly progressive aphasic disorder due to degenerative cortical disease are reported. The length of history varied from 18 months to 6 years. In 5 patients, there was a naming deficit, associated in 4 of these with some abnormalities in comprehension. One patient had a progressive history of reduced speech output, which was associated with an orofacial dyspraxia. All patients were studied neuropsychologically, and in addition regional cerebral metabolism was measured using positron emission tomography. A localized left hemisphere deficit was found in all patients except 1, who had the longest history and the most profound clinical deficit, and who also had right hemisphere hypometabolism. The major brunt of the deficit was in the anterior portion of the left temporal lobe in all but 1 case, the patient with poor speech output who had a more severe left posterior frontal deficit. These findings suggest that in progressive aphasia due to focal cortical atrophy there is heterogeneity in the clinical presentation and anatomical site of the deficit, with possible implications for the underlying aetiology.

INTRODUCTION

Progressive loss of speech due to cortical degeneration has been reported as an initial presentation of a primary degenerative dementia, and as an isolated phenomenon progressing over many years without evidence of more generalized cognitive impairment. Dysphasia is now known to be a common accompaniment of dementia of Alzheimer type (DAT), usually in the presence of other abnormalities, but can present as a prominent early feature (Kirshner *et al.*, 1984; Selnes *et al.*, 1988). Rarely, an isolated progressive aphasia without behavioural change or other cognitive abnormalities, can present as the initial symptom of Alzheimer's disease (Pogacar and Williams, 1984).

In addition to cases of Alzheimer's disease and Pick's disease, in which dysphasia may be an early and relatively isolated feature (Wechsler, 1977; Wechsler *et al.*, 1982), rare cases of progressive isolated dysphasia have been described (Sérieux, 1893; Franceschi, 1908; Rosenfeld, 1909). In 1982, Mesulam reviewed some of these reports, and described 6 further cases of progressive aphasia due to cortical atrophy, of whom 5 had a progressive anomic dysphasia (Mesulam, 1982). A number of authors have addressed the question as to whether or not dysphasia due to focal atrophy is an isolated phenomenon or a prolonged prodromal phase of dementia (e.g., Foster and Chase, 1983; Gordon and Selnes, 1984). The early descriptions of focal cortical degenerations have

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been quoted in more recent reviews (Sérieux, 1893; quoted by Mesulam, 1982) as lending support to the hypothesis that progressive aphasia due to focal cortical atrophy can occur in the absence of a generalized dementia, even when followed over some years. However, the early literature has recently been reviewed by Poeck and Luzzatti (1988), who concluded that of all the 19 patients described up to 1940, only 2 had a relatively pure language deficit at the end of the period of observation.

Serial computerized tomography (CT) scanning in some of these patients has revealed progressive left hemisphere atrophy (Mesulam, 1982). Positron emission tomography (PET) studies of 2 patients with progressive dysphasia showed a localized area of hypometabolism in the left frontotemporal region (Chawluk *et al.*, 1986) without the posterior parietal hypometabolism associated with Alzheimer's disease (Frackowiak *et al.*, 1981).

The question remains as to whether or not progressive aphasia due to focal cortical atrophy is a homogeneous or a heterogeneous entity, in terms of its neuropsychological features, anatomical localization of the deficit, and possible progression to more widespread clinical deficits. In an attempt to address this question, 6 patients with a progressive disorder of speech due to cortical degeneration, with varying lengths of history and differing clinical features, have been studied neuropsychologically and with PET.

CASE REPORTS

Case 1

A 44-yr-old right-handed professional male presented with a 4 yr history of progressive deterioration of memory, which had necessitated his retirement from work. His wife noted that he had become more rigid in his habits since the onset of the illness. He had been blind in the left eye since a childhood injury, but there was no other significant past medical history. His mother had died aged 72 yrs from a dementing illness that had begun in her forties, accompanied by alcohol abuse: there was no histological diagnosis. On examination of the patient, there were no abnormal neurological signs, and speech was fluent and normally articulated. There was no impairment of verbal comprehension; however, his ability to name common objects was definitely impaired. For example, he named a scarecrow a 'bird-deterrer' and a corkscrew, a 'screw'.

On the Wechsler Adult Intelligence Scale (WAIS), he obtained a verbal IQ of 129, and a performance IQ of 121. His NART (National Adult Reading Test) reading IQ equivalent was also 121. On both the verbal and the visual version of the Recognition Memory Test he scored within the average range (words 48/50 correct, faces 40/50 correct). On the Unusual Views Perceptual Test, he scored above the 75th centile. On the relatively easy Oldfield Picture Naming Test, he scored 19/20 correct, whereas on the more stringent Graded Difficulty Naming Test, his score was only 2 items correct. Indeed, the only impairment demonstrated on a wide range of cognitive tests was this very impaired score on the Graded Difficulty Naming Test. Details of all neuropsychological tests quoted are given in the Appendix.

He had previously been found to have slightly abnormal liver function tests with an elevated alkaline phosphatase, but liver biopsy performed at another hospital showed normal histology and copper content. Other investigations, including CSF, nerve conduction studies, visual evoked responses, and small bowel and rectal biopsy were all normal. Electroencephalography (EEG) was normal. CT was normal, but magnetic resonance imaging (MRI) showed left perisylvian atrophy.

Case 2

A 63-yr-old right-handed senior civil servant presented with a 4 yr history of progressive deterioration in his use of language, and comprehension of the spoken word. He continued to work until July 1988 (8 months after first assessment and PET scan) when he took early retirement on account of his 'memory

problems'. He had no significant past medical history, but his mother had apparently been demented for some years before her death at the age of 93 yrs, although without histological diagnosis. There was no other significant family history. He was normotensive, and there were no abnormal signs on general neurological examination. Although he spoke freely and fluently, even volubly, he used a repetitive and limited vocabulary, with frequent circumlocutions. He tended to use expansive gestures while talking. Articulation was normal. Reading and writing were also somewhat impaired. This patient has been reported previously as a case of a category and modality specific comprehension impairment (McCarthy and Warrington, 1988).

On the WAIS, he obtained an average verbal IQ of 95, with a performance IQ of 116. On Set 1 of the Advanced Progressive Matrices, he scored 12/12 correct, which places him above the 95th percentile. On a test of picture recognition memory, he scored close to the 75th percentile, and on a perceptual test (Fragmented Letters) he again scored at 75th percentile. In contrast, on the Graded Difficulty Naming Test he was unable to name any items. On the Oldfield naming test he scored 11/20 correct. Not only were his naming skills significantly impaired, his ability to comprehend single spoken words and single written words was also very poor for a person of his educational background. Thus he obtained a score of 63/150 correct on the oral version of the Peabody Picture Vocabulary test and 79/150 on the written version. On the NART, he obtained a reading IQ equivalent of 95 which is well below his estimated optimum level. In summary, he had moderately severe word retrieval and word comprehension difficulties, in the context of relatively intact nonverbal skills.

Serum biochemistry, including thyroid function tests, and VDRL were normal or negative, as was examination of the CSF. EEG was normal. CT scan of the head was normal, but MRI revealed left perisylvian atrophy, visible only on the coronal slices (fig. 1), not on the transverse slices.

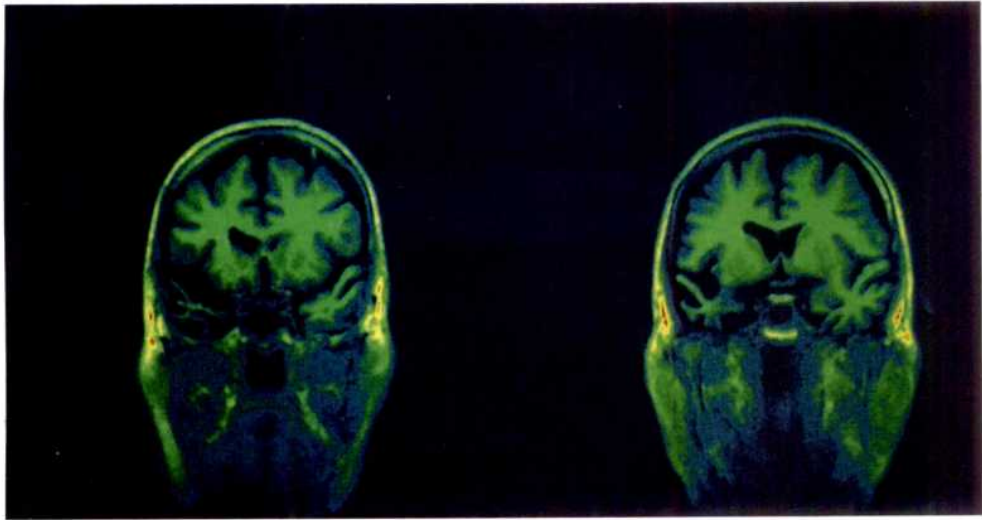


FIG. 1. MRI scan from *Case 2* (coronal slices) showing left temporal lobe atrophy.

Case 3

A 72-yr-old right-handed retired domestic science teacher presented with an 18 month history of progressive impairment of speech, with particular difficulty in finding names. She described some writing difficulties, and an increased need to consult the dictionary for the spelling of relatively simple words. She continued to care for herself adequately, and to drive a car without getting lost. She had been on antihypertensive treatment for 5 yrs, but there was no history of any sudden or stepwise deterioration in her symptoms.

Her mother had died at the age of 55 yrs following a stroke, but there was no family history of dementia. On examination, there were no abnormal neurological signs apart from an equivocal right plantar response, and no praxic difficulties. Cardiovascular examination was normal, with sinus rhythm, a blood pressure of 170/90 mmHg which remained stable with repeated measurements, and no evidence of cardiomegaly clinically or on chest x-ray. Although clearly articulated, marked word-finding difficulties were obvious in her spoken speech. She used circumlocution expressions, but even so, frequent paraphasic errors were noted. She had difficulty naming common objects, but her language comprehension appeared to be intact and she was able to point to named objects.

When first tested on the WAIS (May 1988) she obtained a verbal IQ of 97 and a performance IQ of 101. Her NART reading IQ equivalent was 110, which indicates that this level of functioning was somewhat below her optimum level. On retesting, 4 months later, she obtained a verbal IQ of 85, and a performance IQ of 98. She scored at the 99th percentile for her age on the visual version of the Recognition Memory Test. Her perceptual skills were within normal limits (Fragmented Letters 75th percentile, Unusual Views between the 25th and 75th percentile). Her major difficulty was naming to confrontation. She failed to score on the Graded Difficulty Naming Test, and was only able to name 6 of the items of the Oldfield Picture Naming Test. Her single word comprehension was satisfactory in that she obtained a score of 124/150 on the Peabody Picture Vocabulary Test. She scored below the 5th percentile on the verbal version of the RMT. In summary, she had very marked word retrieval difficulties, and there were no other cognitive deficits of note, other than her impaired verbal memory.

Haematological indices and serum biochemistry were normal, and VDRL negative. CSF was acellular, but the protein content was mildly elevated at 0.63 g/l. Antinuclear factor was positive at a dilution of 1:40, with negative DNA binding. EEG was normal. CT scan showed left hemisphere atrophy, but multiple white matter low attenuation changes, which were also seen on MRI scan. Doppler carotid studies suggested a 50% narrowing on the left, but intravenous digital subtraction angiography (DSA) showed only mild narrowing of the internal carotid arteries bilaterally.

Case 4

A 73-yr-old right-handed housewife had a 2½ yr history of progressive loss of speech, with impaired articulation. She continued to live alone, and found her way around London without difficulty. Her speech output was poor, with effortful and halting production of monosyllabic words, and her sentence construction lacked content. Language comprehension both of the spoken and written word appeared to be intact. There were signs of apraxic difficulties, with inability to mime gestures or to mime the use of common objects. She also had evidence of orofacial dyspraxia, for example being unable to blow a kiss.

She obtained a performance IQ of 89 on the WAIS. Her speech production difficulties were too severe to obtain a reliable verbal IQ. On the Advanced Progressive Matrices Set 1 she obtained above the 50th percentile. On a recognition memory test for pictorial material (Camden A), she scored at the 25th percentile. On the Fragmented Letters Test, she scored at the 25th percentile. She had a very significant naming deficit. She named 3 pictures on the Graded Difficulty Naming Test, and 17/20 on the easier Oldfield Picture Naming Test. Her score on the verbal version of the RMT was below the 5th percentile. She obtained a reading equivalent of 98 (NART) which was considered to be somewhat below her optimum level. She had considerable difficulty in repeating both one syllable words (16/20 correct) and three syllable words (14/20 correct), making numerous paraphasic errors. However, her comprehension of single words was fairly satisfactory. She scored 115/150 on the Peabody Picture Vocabulary Test. In summary, she had moderately marked speech production difficulties, and quite severely impaired word retrieval difficulties, in the context of satisfactory word comprehension and nonverbal cognitive skills.

Physical examination was normal, with no abnormal neurological signs and normal blood pressure. Serum biochemistry, full blood count and ESR were within normal limits. EEG was normal, as was CSF examination. CT scan showed mild generalized atrophy.

Case 5

A 56-yr-old retired right-handed fireman gave a 2 yr progressive history of difficulty 'remembering words'. At presentation, reading had become impossible. His speech was normally articulated and fluent, but empty of content. He had a profound nominal dysphasia, and was unable to comprehend simple instructions. He was able to describe objects, for example, when shown a ruler, he said 'I quite often

use that. You do it to see how far it is.' He was unable to read and write. Nevertheless, he continued to manage the family finances, and was able to do complex jigsaw puzzles. There was no evidence of dyspraxia or of visuospatial difficulties, and he could perform simple calculations, including fractions and subtracting serial sevens.

He was tested on the vocabulary subtest of the WAIS and obtained a scaled score of 3 (defective). By contrast, on the Block Design subtest of the WAIS he obtained a scaled score of 13 (high average). On the Standard Progressive Matrices, he obtained a score of 48/60 which is above the 95th percentile for his age. His perceptual functions were satisfactory. He identified 19/20 Fragmented Letters. On the Oldfield Picture Naming Test he was only able to name one item. In addition, his comprehension was quite impaired. On the Peabody Picture Vocabulary Test, he failed to obtain the basal level of getting the first 8 items correct (a level easily obtained by a 2-yr-old child). His reading was also impaired, and he failed to score on the NART. There was no speech production difficulty, insofar as he was able to repeat polysyllabic words, sentences and clichés quite satisfactorily. In summary, he had severe word retrieval and word comprehension difficulties, his nonverbal reasoning abilities being excellent.

Neurological examination was normal, with normal blood pressure. Haematological and biochemical investigations were normal, apart from a weakly positive ANF (1:40). CSF examination was noncontributory. CT scan showed a focal area of atrophy at the anterior pole of the left temporal lobe.

Case 6

A 66-yr-old right-handed retired stockbroker's clerk had a 6 yr history of progressive language impairment. One yr after onset, he was found to have a nominal dysphasia with impaired sentence construction and reading. Memory and reasoning were intact. By 1985, after 3 yrs of illness, he could only utter 2–3 words at a time, and by 1987 was using single words only. When assessed at the time of scanning (1988), he had no spontaneous speech at all, and his only vocalization was high pitched grunting. He appeared to have no understanding of speech, and his writing was limited to at most 2–3 words at a time. His ability to comprehend written words was very limited, although he sometimes appeared to understand what his wife wrote down for him. At one point, while being assessed in his wife's absence, he became quite distressed and repeatedly wrote 'Alice—understained—mind' (sic). According to his wife, he could dress himself, wash and shave alone, and do the gardening without prompting, and helped with the housework. He continued to sign cheques, and drove a car locally without getting lost. He recognized family and friends, and appeared to follow football and snooker matches on television. He was able to communicate in a rudimentary way with his wife by signs, for example holding up fingers to demonstrate which number channel he wanted to watch on television. At his most recent assessment, he did not appear to have any understanding of simple gestures, although previously it had been possible to communicate with him using signs. His behaviour changed during the 5 yr period of observation, becoming somewhat disinhibited, and with the use of overenthusiastic, even bizarre gestures. Physical examination was normal, apart from the presence of snout, pout and grasp reflexes.

The original assessment of this patient was carried out in 1983, when he obtained a verbal IQ of 85, with a performance IQ of 110. On reassessment later that year, he was no longer able to cope with the task demands of the verbal scale of the WAIS, but was still able to obtain a performance IQ of 104. His performance IQ remained steady in the upper half of the average range on repeated testing, until 1986. However, because of the deterioration in his verbal skills, more especially the deterioration in his comprehension of language, it became impossible to carry out the formal assessment on the WAIS. He appeared not to understand the simplest instruction, and he was unable to reach a basal level on the Peabody Picture Vocabulary Test: he failed 3 of the first 8. Not only was he unable to name any items from the Graded Difficulty Naming Test, he was unable to name any items from the Oldfield Picture Naming Test. Indeed, no examples of meaningful speech were recorded. Nevertheless, when he finally realized the nature of the problem, he scored at the 70th percentile for his age on the Colour Matrices, indicating that in spite of his grave language impairments, his capacity for nonverbal reasoning may have been relatively intact. In summary, he had the most profound dysphasia: his word retrieval and word comprehension capacities appeared to be totally obliterated.

Haematological and biochemical investigations were normal, as was EEG. CT scan showed widening of the left sylvian fissure, and a small left middle fossa arachnoid cyst, which was not thought clinically relevant, and showed no change on serial scanning.

METHODS

^{15}O steady-state positron emission tomography (PET) scans were performed on the CTI/931/12/8 (CTI, Tennessee, USA) scanner at the MRC Cyclotron Unit at the Hammersmith Hospital, to obtain regional values of CMRO_2 (cerebral metabolic rate for oxygen). The performance characteristics of this scanner have been described (Spinks *et al.*, 1988). Ethical approval for these studies, and for normal studies on 9 volunteers (aged 32–74 yrs), was obtained from the Ethical Committees of St Mary's, the National and Hammersmith Hospitals. Approval to administer radiolabelled gases was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom. Written consent was obtained from all patients, and normal volunteers, after a full explanation of the procedure.

Normal subjects had no abnormalities on physical examination, and a normal blood pressure. They scored at least 28/30 on the mini-mental state examination (Folstein *et al.*, 1975). Subjects with a history of seizures, significant head injury, hypertension, or neurological or other systemic disease were excluded.

Patients and subjects were positioned on the scanning bed, with the head symmetrically aligned along the orbitomeatal line, resting in an individually made rigid polyurethane foam head mould. Careful observation of the patients and subjects throughout the scan ensured that there was no significant head movement. A 22 gauge plastic cannula was inserted into the radial artery at the wrist, after subcutaneous infiltration of long acting local anaesthetic (bupivacaine 1%). After a 15 min transmission scan ($\text{Ga}^{68}\text{Ge}^{68}$), two consecutive emission scans were performed during inhalation of C^{15}O_2 and $^{15}\text{O}_2$, respectively, at steady state, with a 10 min wash-out period between each scan. Finally, a further 6 min scan following 4 min of C^{15}O inhalation, and equilibration for 1 min, was collected. After correction of the emission scans for attenuation, they were transformed into parametric images, using the arterial oxygen content and whole blood and plasma activities, measured in triplicate, during C^{15}O_2 , $^{15}\text{O}_2$, and C^{15}O scanning. Thus 4 quantitative data sets of CMRO_2 , cerebral blood flow (CBF), oxygen extraction ratio (OER), and cerebral blood volume (CBV) were obtained. Details of this method, and the cerebral blood volume component, have been described previously (Frackowiak *et al.*, 1980; Lammertsma and Jones, 1983; Lammertsma *et al.*, 1983).

Images were inspected to ascertain the presence and position of the focal deficits. Images were presented as 15 planes of data with a resolution of $8.5 \times 8.5 \times 7$ mm after reconstruction, with no interplane deadspace. Using a Sun 360 computer and image analysis software 'Analyze' (BRU/Mayo Clinic), images were also inspected in the coronal and sagittal planes following a 1:3 linear interpolation in the vertical axis (z plane), which generated 43 images, and rendered the voxels approximately cubic.

Anatomical localization was obtained with reference to the atlas of Talairach *et al.* (1967). A line was drawn on the sagittal image along the intercommissural line joining the anterior and posterior commissures (AC-PC line). Each CMRO_2 image was then reorientated so that it lay horizontally parallel to the AC-PC line, and therefore compatible with the orientation of the stereotactic atlas. This method of anatomical localization has been described previously (Friston *et al.*, 1989). The errors inherent in using a localization technique are small compared with the variations in the shapes of individual brains (Friston *et al.*, 1989) (although there may be some uncertainty using a method based on a stereotactic atlas in patients with focal atrophy). The technique is based on the method of Fox *et al.* (1985), with the advantage that cross-referencing to skull x-rays for anatomical positioning is obviated. The width, length and height of each brain was measured and used to transform the stereotactic coordinates from the anatomical atlas on to the appropriate regions on the CMRO_2 images. The anatomical sites of the focal physiological deficits were thus identified.

Numerical data were obtained using a circular region of interest (ROI) of diameter 8 mm (approximately 1 resolution element), which covered the visible cortical ribbon. Visual inspection indicated that the areas of maximal hypometabolism were restricted to left frontal and temporal lobes. Regions of interest were therefore placed on the anterior, middle and posterior frontal gyri, and the superior, middle and inferior temporal gyri in the right and left hemispheres. Readings were taken from those scan planes which corresponded exactly to the anatomical reference planes, according to the distance above or below the AC-PC line. This meant that each structure was sampled with 4 ROIs, from 4 adjacent anatomical planes (the 4 lowest planes on the atlas, on which all these structures are visible). The mean value for a given structure is presented. In addition, cerebellar cortex was sampled from the same planes, and parietal cortex from 3 representative planes distant from the sites of frontal or temporal hypometabolism. Measurements were made from the left and right hemisphere independently.

RESULTS

The aim of the study was to detect metabolic changes. The results of the CMRO₂ data are therefore presented. CBF and OER data showed coupled changes in flow, with a fractional oxygen extraction that did not differ from normal. CMRO₂ images for all 6 patients, with a normal for comparison, are shown below (fig. 2). Left-right asymmetry is obvious in at least some of the lower slices in all cases. In Case 1, the asymmetry is only visible on the most inferior slices, while the asymmetry in Case 4 is situated more anteriorly than the others.

The areas of hypometabolism on the PET scans appeared more extensive than visible areas of atrophy on the CT or MRI scans. The scans were performed for clinical purposes at another centre and were not aligned in the same way as the PET scans, but considerations of resolution made comparisons relatively easy. Fig. 3 shows 4 low transverse MRI slices from Case 2, with 4 low transverse PET slices for comparison. No atrophy is visible on the MRI images, in marked contrast to the PET images. Despite the absence of direct comparability, the MRI images cover much the same volume of brain as the PET slices, and suggest that the area of hypometabolism on the PET image is much more extensive than any visible atrophy on the structural image. Dissociation between visible atrophy on a structural image and hypometabolism is not uncommon, for example the characteristic biparietal hypometabolism of DAT may occur in the absence of visible cortical atrophy on CT or MRI scan.

CMRO₂ values for the individual cases, and for the normal subjects are shown in the Table. The values for the normal subjects are given as mean values for the whole population with SDs. Values marked with an asterisk are outside 2 SDs of the normal population, i.e., outside the 95% confidence interval ($P < 0.05$). Results for individual patients are illustrated graphically (figs. 4, 5).

Maximal left hemisphere hypometabolism occurred in all patients, except Case 4, in the superior temporal gyrus; in Case 4, the maximal reduction was more anterior, in the posterior frontal gyrus. Right hemisphere hypometabolism was present in Case 6, who had the most profound reduction in metabolism, affecting both left and right hemispheres.

DISCUSSION

The CMRO₂ values obtained in these patients show normal right hemisphere metabolism in all patients, apart from Case 6. Case 6 has the longest history, and the most severe deficit. Cases 1, 2, 3 and 5 all had predominant naming difficulties, and all have the most severe deficit in the left superior temporal gyrus. Case 1, with an almost isolated naming deficit, had abnormally low metabolism in the anterior portion of the superior temporal gyrus alone. Cases 2, 3 and 5 all had more severe neuropsychological impairments, including abnormalities other than naming. This is reflected in a more widespread abnormality of cerebral metabolism affecting the third frontal gyrus on the left and all of the left temporal lobe. Case 4, on the other hand, who had a prominent word production difficulty associated with orofacial dyspraxia, associated with apparently normal verbal comprehension, exhibited a more anterior deficit. Case 3 showed widespread involvement of the left hemisphere, including the parietal lobe, but right hemisphere metabolism was normal.

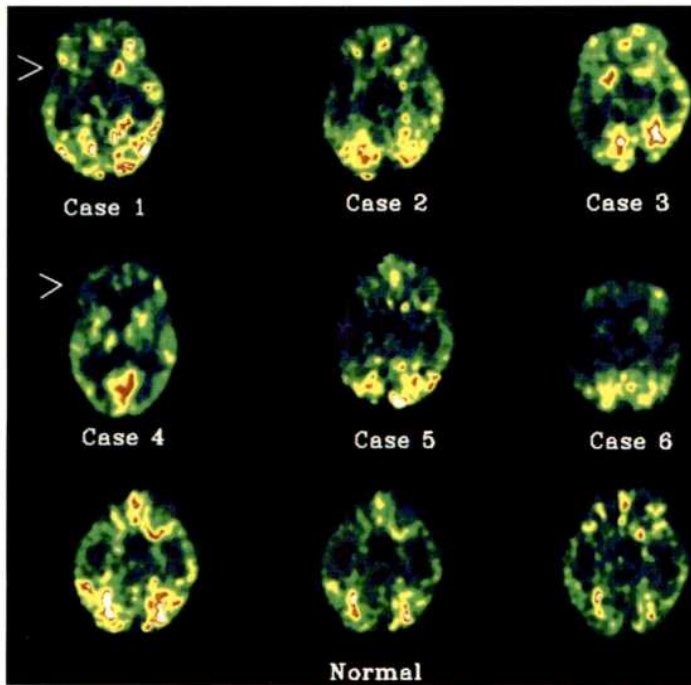


FIG. 2. CMRO₂ scans from Cases 1–6, with 3 slices from a normal scan for comparison. Visible areas of asymmetry for Cases 1 and 4 are marked with an arrow. Slices shown for Cases 1, 2, 3, 5 and 6 are 0.5 cm below the intercommisural (AC-PC) line, and for Case 4, 0.1 cm above the AC-PC line. The 3 normal slices are at 0.5 cm below, 0.2 cm below, and 0.1 cm above the AC-PC line. Each scan is scaled to its own maximum.

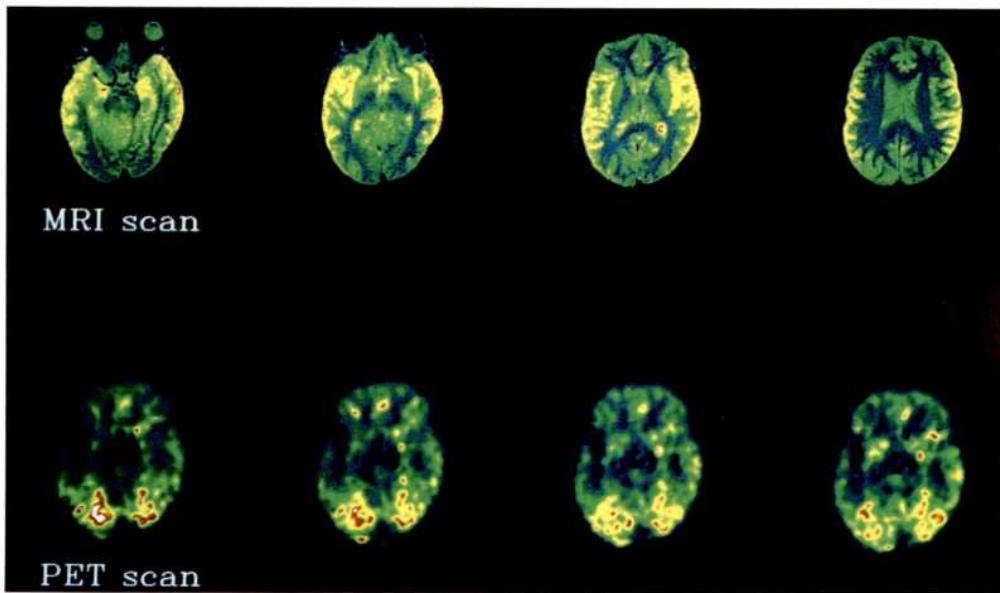


FIG. 3. Transverse slices of MRI scan and CMRO₂ scan from Case 2, showing hypometabolism which is not matched by atrophy on transverse MRI slices (*see text*).

TABLE CMRO₂ VALUES

CMRO ₂ (ml·min ⁻¹ ·dl ⁻¹)	Normal (±SD)	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
L ant. frontal gyrus (F1)	2.82±0.22	2.59	2.48	2.74	2.57	2.8	1.86*
R ant. frontal gyrus (F1)	2.93±0.26	2.61	2.76	2.81	2.64	2.61	1.77*
L mid. frontal gyrus (F2)	2.56±0.36	2.58	2.05	2.32	2.51	2.39	2
R mid. frontal gyrus (F2)	2.71±0.42	2.87	2.38	2.28	2.75	2.75	1.97
L post. frontal gyrus (F3)	2.80±0.34	3.13	1.35*	2.04	1.91*	1.81*	1.18*
R post. frontal gyrus (F3)	2.89±0.33	2.71	2.35	2.12	2.59	3.19	1.89*
L sup. temporal gyrus (T1)	2.93±0.20	1.93*	1.12*	1.67*	2.1*	1.22*	0.93*
R sup. temporal gyrus (T1)	3.04±0.22	2.99	2.83	2.36	2.43	2.86	1.76*
L mid. temporal gyrus (T2)	3.08±0.37	2.94	2.01*	1.73*	2.3	1.87*	1.34*
R mid. temporal gyrus (T2)	3.08±0.25	2.99	2.67	2.44	2.6	2.83	1.97*
L inf. temporal gyrus (T3)	3.18±0.21	3.2	2.58*	1.76*	2.83	1.99*	1.48*
R inf. temporal gyrus (T3)	3.19±0.39	3.31	2.73	2.51	2.72	2.85	2.34
L parietal cortex	3.20±0.19	3.15	2.88	1.87*	2.74	2.88	1.5*
R parietal cortex	2.99±0.29	2.99	3.06	2.71	2.74	2.89	1.88*
L cerebellum	3.72±0.39	3.91	3.91	3.07	3.31	4.18	3.18
R cerebellum	3.64±0.51	3.9	3.9	3.12	3.28	4.14	3.04

CMRO₂ values for the 9 normal subjects, for the different regions, with 1 SD about the mean given in brackets, together with the values for each of the patients. Values marked with an asterisk are significantly different from controls ($P < 0.05$), i.e., outside the 95% confidence interval.

Despite the severity of the language deficit, all the patients, including Case 6, were able to live at home, to care for themselves adequately, manage their financial affairs, and even to drive without difficulty. None of them demonstrated the loss of social skills which is often associated with generalized dementing disorders (McKhann *et al.*, 1984). Cases 1, 2 and 6 were reported by their spouses to have become somewhat obsessional in their habits, and Case 6 appeared to have become slightly disinhibited in his use of gesture, but all the patients had appropriate social behaviour.

The underlying aetiology in our patients remains uncertain. In all of them, the history was gradually progressive, suggesting a degenerative process rather than vascular disease. Case 3 was being treated for hypertension, and had minor white matter signal changes on MRI. DSA and Doppler sonography showed internal carotid artery narrowing, which was less than 50%. However, the very progressive nature of her history argues strongly against multiple small cortical or subcortical infarctions as a cause of her symptoms. The small left middle fossa arachnoid cyst in Case 6 caused no mass effect, and is considered irrelevant. In the other cases, CT and/or MR scanning showed mild generalized (Case 4), or left perisylvian, atrophy (Cases 1, 2 and 5), sometimes (Case 2) discernible only on coronal reconstruction.

Alzheimer's disease is common, and could be responsible for the changes in some or all of our patients. However, although language disorders are frequently associated with Alzheimer's disease, in all our patients the histories of relatively isolated language disorder are atypically long. The case of focally presenting Alzheimer's disease described by Pogacar and Williams (1984) had evidence of nonverbal cognitive dysfunction 12 months after the onset of symptoms. Further, EEGs in all our cases were normal, in contrast to the common finding of slow wave abnormalities in early DAT.

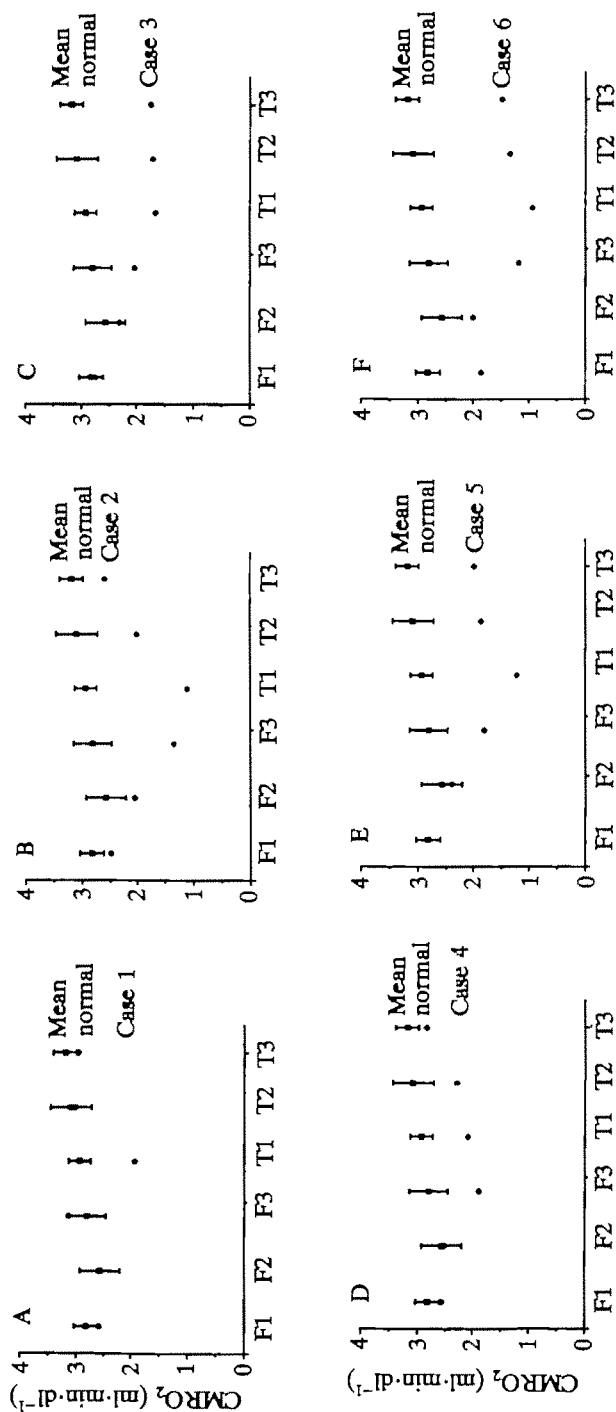


FIG. 4. Left hemisphere cortical plots for each of the 6 patients (A-F, Cases 1-6, respectively). The mean of the normals is also shown, ± 1 SD. $CMRO_2$ values are shown on the y axis, with the sample regions (F1, F2, F3, T1, T2, T3) plotted on the x axis. Some values for some of the patients are outside a single SD, but still within the 95% confidence limit, and so not significantly different from controls.

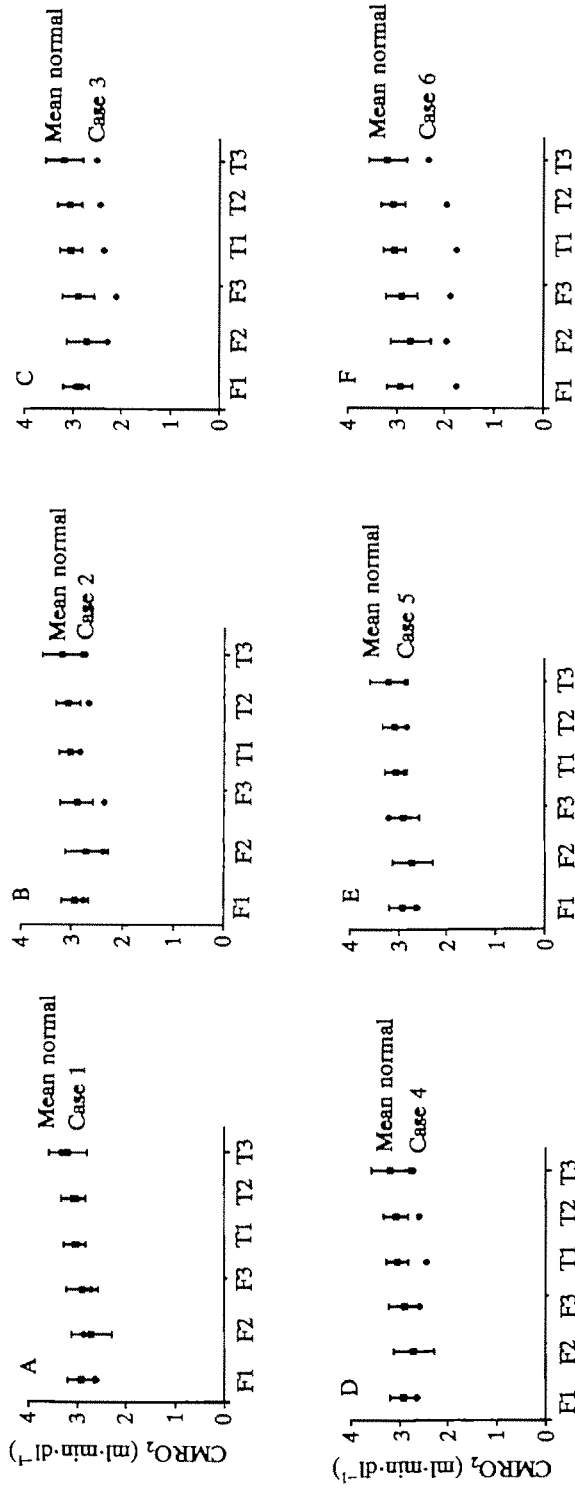


FIG. 5. Right hemisphere cortical plots for each of the 6 patients (A-F, Cases 1-6, respectively)

The underlying pathology may be similar in one or more of our cases to that described by Kirshner *et al.* (1987), in 2 patients with progressive dysphasia in whom a nonspecific, focal, spongiform degeneration restricted to the left frontal or temporal cortex was found. It would seem unlikely, on clinical grounds alone, that any of them are suffering from the frontal lobe dementia described by Gustafson (1987), unilateral Creutzfeld-Jakob disease (Yamanouchi *et al.*, 1986; Mandell *et al.*, 1989) or the hereditary dysphasic dementia of Morris *et al.* (1984). In any event, it is likely that the pathology underlying focal cortical atrophy is heterogeneous, and may be due to previously unrecognized cortical degenerations, or represent part of a spectrum along which lie the other more clearly described and recognized disorders. Although the clinical presentation in our cases is relatively unusual, there is no reason to believe that a particular clinical presentation would point to a specific pathology. Likewise, the clinical presentation may give little information about the eventual progression to generalized mental deterioration; this has been discussed in detail by Mesulam (1987).

The interest in the PET data is the localization of the anatomical site of maximal hypometabolism in a way not possible with MRI or CT scanning. In addition, none of our patients showed either the characteristic pattern of posterior biparietal and biparietal hypometabolism of DAT (Frackowiak *et al.*, 1981), or the bifrontal hypometabolism associated with the frontal lobe dementias (Gustafson, 1987; Neary *et al.*, 1988). Chawluk *et al.* (1986) described ^{18}F -deoxyglucose scans in 2 patients with 3 yr histories of progressive dysphasia. One patient showed left temporal hypometabolism, while the second had abnormalities most marked in the parietal association cortices. No regional deficits were found in the right hemisphere, and overall absolute glucose metabolic rates were equal to or greater than control values. The authors concluded that there was no evidence, either neuropsychologically or from the PET scan findings, of more widespread deficits that might suggest a generalized dementing illness. Both patients in this study had similar lengths of history, and similar clinical deficits. Although predominant left hemisphere metabolic dysfunction has been described in dementia (Loewenstein *et al.*, 1989), right hemisphere metabolism is usually also affected, although sometimes less so than the left.

The correlation of clinical abnormality and focus of hypometabolism in our patients is of interest. Naming difficulties were the common features of all these patients, indeed the only deficit in Case 1. All our patients share a metabolic deficit in the left temporal lobe. This is entirely consistent with group data that implicate the temporal lobe in word retrieval skills (Coughlan and Warrington, 1978; Kertesz *et al.*, 1979).

Case 4 showed maximal change in the frontal cortex, consistent with her speech production deficit. Increasing clinical severity is associated with extension of the deficit beyond the left frontotemporal region. Case 6 is the only one to reveal right hemisphere deficits comparable with, though less marked than, those on the left, with maximal abnormality in the anterior temporal lobe, rather than its posterior part which is associated with DAT (Frackowiak *et al.*, 1981). The extension to the contralateral right temporal lobe may be due to transcallosal connections providing a route for transfer of a pathogenic agent, or as a result of transsynaptic degeneration. Alternatively, there may be intrinsic vulnerability of the anterior temporal cortex to the particular (though unknown) pathogenic agent in that particular patient. The symmetry of the hypometabolism in Case 6 is reminiscent of the patient described by Mingazzini (1914), who also showed symmetrical

atrophy in the two superior temporal gyri. It is tempting to suggest that there may be a transcallosal progression or extension of disease from one area to its contralateral homologue. However, histological studies in monkey fail to show any transcallosal fibres connecting the anterior temporal poles (R. E. Myers, 1965; quoted by Brodal, 1981), and data using the horseradish peroxidase technique in mammals (including subhuman primates) also fail to show transcallosal connections between these areas (Innocenti, 1986).

The selective vulnerability of the left anterior temporal cortex requires an explanation, as no clear cases of equivalent isolated right temporal lobe degeneration have been described. This may be an artefact of the clinical eloquence of language disturbance. There are biochemical differences between dominant and nondominant temporal lobes (Sorbi *et al.*, 1984), but these are not prominent. It is therefore possible that certain types of neuronal degeneration may have a predilection for particular patterns of neuronal wiring or histological cell type. Such speculation offers a tentative explanation for the relative anatomical selectivity of the cortical degeneration.

Although the length of follow-up in some of our patients is relatively short, Case 6 had been assessed neuropsychologically over a period of 6 yrs, and both Cases 1 and 2 had 4 yr histories; it is noteworthy that despite the similar length of history in these 2 patients, Case 2 had a much more profound deficit and more widespread involvement on the PET scan, than Case 1.

These cases reflect the variety of clinical presentations that may be associated with progressive dysphasia without dementia due to focal cortical atrophy. The different clinical presentation of Case 4 is reflected in the different site of maximal hypometabolism. The other cases were similar in that they all shared a naming deficit as one of their presenting features, but the varying length of history and clinical severity is reflected in the extent of the hypometabolism. These cases underline the differences between patients in the course of the disease, and the anatomical site of the pathological process. It is not possible to predict the underlying histological disorder from the clinical, neuropsychological and anatomical data, but the clinical and anatomical heterogeneity may reflect heterogeneity of the causative pathological processes.

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APPENDIX

Description of the tests referred to in the case reports

Wechsler Adult Intelligence Scale (WAIS). The verbal IQ was prorated from the scores on 4 subtests (Vocabulary, Similarities, Arithmetic and Digit Span). The performance IQ was prorated from 3 subtests (Block Design, Picture Completion and Picture Arrangement).

National Adult Reading Test (NART). This test consists of 50 irregularly spelled words covering a wide frequency range (Nelson, 1982).

Progressive Matrices. There are 3 versions of Progressive Matrices, a graded difficulty nonverbal reasoning test.

- (1) Standard Progressive Matrices 5 sets of 12 problems
- (2) Advanced Progressive Matrices, set 1, 12 problems
- (3) Coloured Progressive Matrices, 3 sets of 12 problems (Raven, 1938).

Recognition Memory Test (RMT). This test consists of a verbal version (50 words) and a visual version (50 faces), which are tested in a forced choice of 2 (Warrington, 1984).

The Oldfield Picture Naming Test. A shortened version of this relatively easy naming test consists of 20 line drawings of objects, including 6 very common names (Oldfield and Wingfield, 1965).

Graded Difficulty Naming Test. This stringent naming test consists of 30 line drawings of objects spanning a wide frequency range: even the easiest items (kangaroo, scarecrow) are relatively low frequency words (McKenna and Warrington, 1983).

Peabody Picture Vocabulary Test. This is a word-picture matching test for which developmental norms for ages ranging from 2–18 yrs are available (Dunn, 1959).

Perceptual Tests. (1) The unusual views test consists of 20 photographs of common objects photographed from unusual angles. (2) The fragmented letter test consists of 20 letters degraded by photographing through a random noise pattern (Warrington and James, 1988).

DEVELOPMENTAL DYSMNESIA IN A POOR READER

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SUMMARY

A 22-yr-old subject with moderate developmental dyslexia experienced poor memory from an early age. In spite of normal intelligence he had great difficulty in learning historical and geographical names, mathematical formulae, poems and songs, and verbal series such as the letters of the alphabet and the months of the year. His recognition of familiar faces was also faulty at times. A battery of memory tests confirmed a moderate deficit of verbal as well as visual memory, whereas spatial memory was preserved. Other cognitive functions were intact, except for a mild reading disability. No evidence of brain pathology was provided by his history, neurological examination and CT scanning.

INTRODUCTION

It has long been recognized that there are individuals without gross neurological or psychiatric disorders who fail to develop harmoniously some mental skill and who from an early age show an impairment of one or more cognitive abilities, quite out of proportion to their general intellectual level. Most of these selective deficits are subsumed under the heading of learning disabilities and become apparent when the child is confronted with academic requirements, such as reading, writing, spelling and arithmetic. An inadequate development of basic skills is also recognized for the acquisition of language (developmental aphasia), of motor skills (developmental apraxia; Cermak, 1985) and of finger recognition coupled with acalculia and other features of the Gerstmann syndrome (Kinsbourne and Warrington, 1963; Benson and Geschwind, 1970; PeBeaito *et al.*, 1988). A case of congenital impairment for the recognition of familiar faces is on record (McConachie, 1976). We report here a patient who from an early age experienced poor memory and mild dyslexia, in spite of a negative perinatal and subsequent history, normal neurological development and a good level of general intelligence.

CASE HISTORY

M.S., a 22-yr-old right-handed man, came to the outpatient clinic at the Modena University Department, asking whether doctors knew of disorders similar to those of which he had been complaining since childhood, and which had formerly been attributed to emotional problems. He had seen a television programme on brain function and thought that he had recognized his difficulties in some of the conditions that were presented. His main complaints concerned reading and memory. He was the second of 2 children and was born at the end of the seventh month of gestation after a normal pregnancy and a regular delivery. His wt at birth was 2500 g. His developmental milestones were normal, with independent walking at 10 months, first words at 12 months and bladder control at two and a half yrs. Speech development caused no concern. At 5 yrs he was run over by a scooter and had a mild head injury without loss of consciousness or neurological

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sequelae. His problems began when he attended elementary school, where he behaved in an unruly way and showed difficulty in learning to read. These problems did not cause great concern to his parents, however, partly because they were absorbed by their jobs and partly because it was apparent to them that the child was bright and that his lack of discipline was a reaction to the bad attitudes of the teacher, who was an old and authoritarian woman. Yet his reading and writing disability persisted even when the teacher was changed and at the end of the elementary course he was practically unable to read and wrote very imperfectly. The final evaluation given by his teachers was 'We have been unable to understand the nature of the intellectual disorder shown by this child in his written exercises. His oral performance is much more positive. He is a touchy, fretful and insecure child, who can, however, express logical, wise and mature judgements'. At the end of junior high school, the teachers commented that 'He is interested and participates in school activity although in an intermittent and untidy way. He often exhibits an astonishing intuition, capacity to argue and a mature mind. He reads and writes, however, with difficulty'. His reading disability contrasted with his skilfulness not only in mechanical work, but also in drawing and, when he had to leave a message to his relatives, he used to sketch it out. He continued high school studies and passed the leaving examination. Reading abilities improved and he is now able to read and actually reads a few newspaper articles, but laboriously and slowly.

Although his reading difficulty was the main concern expressed by his teachers, he himself was well aware that his chief problem in learning concepts as well as in everyday activity was verbal memory. Foreign language words, historical and geographical names, and mathematical formulae could barely be memorized and he never succeeded in learning by heart a poem or song. Proper names were particularly difficult. For instance, he claims not to be able to recall more than 15 first names and surnames of his relatives and closer friends, and at times even their evocation is blocked. He may pay a visit to a friend and be unable, much to his embarrassment, to recall his name when he is asked whom he is looking for. 'It is as if a curtain would fall in front of my mind and I may become unable to remember even my brother's name.' He frequently resorts to verbal associations to improve the retrieval of a name. 'There is a girl I know very well, whose name is Roberta. I must recall that she has the same name as my brother (Roberto). For another girl, whose name is Vittoria, I think of the book 'War and Peace' and associate victory with it'. He never succeeded in learning multiplication tables, except for those involving 2, 5 and 10. When asked how much is 7×8 , he proceeds as follows: $7 \times 10 = 70$; $2 \times 7 = 14$; $70 - 14 = 56$. He is unable to recite the letters of the alphabet and the months of the year. For the former he arrives with difficulty at the letter F, and then says 'I know that nearby there are H, L and G ... then the others', but he cannot establish whether M comes before R, or S before V. As to the months, he knows that the first is January and the last December but not the names in between. Asked in which month we are, he replies 'I know it is the fifth', but cannot say May. Also names of the seasons and the day in which they begin are ignored. He forgets appointments and errands and uses notes and asks people to remind him what he has to do. He comments that 'the greatest misfortune that could befall me would be to lose my notebook'.

Although his difficulties mainly concern verbal material, he is also poor at remembering faces. He may not recognize people who greet him and talk to him, although he recognizes them as being familiar. One day, for example, he met a woman at a party who had been his schoolteacher for a few years and chatted for a while, wondering who she was, until she mentioned some details of his schoolmates. He is very keen on the cinema, but admits with a smile that he can see the same motion picture more than once, since he easily forgets the plot. For instance, he was enthusiastic about the film 'The Unbearable Lightness of Being' to the point of seeing it 4 times, but could only vaguely and after some delay report that the story took place in an Eastern European country and concerned a young man who had many girls. His elder brother confirmed that his family has always been aware of his poor memory and the tricks to which he had to resort to keep up appearances and conceal his forgetfulness. He is now employed as a municipal worker.

Neurological examination showed no abnormality. A routine EEG showed an irregular and unstable alpha rhythm (8–9 Hz), reactive to eye opening. Bursts of theta and delta waves were seen bilaterally with a marked prevalence in the left frontotemporal area. A CT cranial scan was normal.

M.S. is a lively, friendly and outgoing young man, who has clear insight into his cognitive weaknesses and was eager to cooperate with the examiner to clarify their nature.

NEUROPSYCHOLOGICAL EXAMINATION

M.S. was given a number of tests to assess more precisely his performance in different cognitive areas. Some of them have been used in previous studies on large samples of normal controls and brain-damaged patients, and a cut-off score discriminating a normal from a pathological performance was available. In addition a matched control group of 10 young men of approximately the same age (range 20–24 yrs) and the same educational level (13 yrs of schooling) was tested.

Intelligence

His Wechsler-Bellevue IQ was 110 for the verbal and 111 for the performance score. His weighted score on the vocabulary subtest was 14. On Raven Progressive Matrices 1938 he gave 53 correct responses out of 60.

Oral language

Many hours of conversation failed to show any sign of impairment in comprehension and speech. He was able to express his thoughts clearly with a rich and appropriate lexicon. He scored 34/36 on the Token Test and 74/85 on the Boston Naming Test. On the Peabody Vocabulary Test he achieved a score of 138, which corresponds to the 97th centile according to the norms for 18-yr-old subjects (Dunn, 1965). He was also given 2 verbal fluency tasks that have been standardized by Novelli *et al.* (1986) in 320 normal subjects. One is semantically cued and requires the subject to retrieve as many exemplars as possible pertaining to the categories of fruits, animals and makes of car. The other is phonetically cued and requires the subject to produce as many words as possible beginning with F, P and L. Each trial lasts 1 min. On both tasks M.S. achieved a score (sum of the three trials) of 46, which, when adjusted for age and years of schooling, is above the means for normal subjects reported by Novelli *et al.*

Written language (see Table 1)

M.S. read 100 out of 120 words correctly. However, for 2 of them reading was slow (more than 5 s, up to a maximum of 12 s) and for 18 other items correct reading was preceded by wrong attempts. In matched controls no more than 1 error preceded correct reading. Reading 50 legal nonwords was correct in 10 s for 23 items and after wrong or partial attempts for 25 other items. Two items were failed. The matched controls' worst score was 43.

TABLE 1. READING AND WRITING TESTS

	M S	Matched controls' cut-off score
Word reading	100/120	119/120
Nonword reading	23/50	43/50
Word writing	102/120	119/120
Nonword writing	46/50	48/50
Reading comprehension	41/50	39/50
Automatized naming		
Two stimulus set	40 s	42 s
Three stimulus set	50 s	54 s

The same lists of words and nonwords were dictated. He wrote correctly 102/120 words and 46/50 nonwords. Errors were substitution, omission or addition of a single letter. In 7 cases they were substitution of a 'b' with a 'd' or vice versa and in one case of a 'p' with a 'q'. On reading 16 numbers of 1, 2 or 3 digits he made 2 errors, both of inversion (36 for 63, 398 for 389). With numbers of 4 or 5 digits, he was very slow (up to 45 s) and succeeded only after wrong attempts. Number writing was correct for 21/22 items. The error was an inversion between 32 and 23.

Written comprehension was assessed with a reading text developed as part of the International Association for the Educational Achievement (IEA) crossnational study of academic achievement (Thorndike, 1973).

The test consists of 8 reading passages and 50 multiple choice questions, requiring specific information about each passage and the ability to draw inferences from the passage and to determine the writer's purpose and point of view. It was given by Lindgren *et al.* (1985) to Italian and American fifth-graders in a crossnational study aimed at assessing the incidence of developmental dyslexia in the two countries. The mean score for the Italian sample was 32.71 (SD 7.25). M.S. scored 41. The matched controls' lowest score was 39 and their mean was 44.

M.S. was also given a test of rapid alternating stimulus naming, designed by Wolf (1986) to assess the automatized processes required for fluent reading. Briefly, he was requested to name as quickly as possible 50 stimuli arranged in 5 rows of 10 stimuli each on a white card. In the two-set format, stimuli were 5 letters and numbers, repeated in a fixed A-B-A-B pattern; in the three-set format, they were 5 letters, numbers and colours, repeated in a fixed A-B-C-A-B-C pattern (for further details, see Wolf, 1986). He performed the two tasks in 40 s and 50 s, respectively, with one self-corrected error for the first second task. Both scores are within the range of matched controls performance and point to a normal retrieval speed and the absence of attentional problems.

Arithmetic

M.S. could easily determine which of 2 numbers having an equal number of digits was higher. He made no error on 7 written additions, 1 error on 7 written subtractions, 5 errors on 7 written multiplications and no error on 7 written divisions. It took him, however, 8 and 10 min, respectively, to carry out the last two types of tasks.

Right-left orientation

M.S. admitted to some difficulty in discriminating between left and right. On Benton's right-left orientation test, form A, he scored 16/20, just below the 17-20 point range which comprises the 96th centile of the normal subjects' performance (Benton *et al.*, 1983).

Finger recognition

M.S. scored perfectly (60/60) on Benton's finger localization test (Benton *et al.*, 1983), when he pointed to the touched finger(s), although 5 errors were made in the verbal identification of the 3 middle fingers.

Constructional praxis

M.S. reproduced correctly 10 geometric designs and produced acceptable drawings of a man, a house, a bicycle and a watch on verbal command.

Visual perception

M.S.'s good performance on the Boston Naming Test is evidence that he had no problem in recognizing object drawings. More difficult tests, such as Ghent's overlapping figure test and Street's incomplete figure test were passed almost flawlessly (36/36 on the former and 9/11 on the latter).

Verbal memory (see Table 2)

M.S. was given the following tests. (1) Digit forwards and digit backwards. (2) Logical memory: immediate and 10 min filled delay recall of a story. The score was the sum of the idea units reported in two trials.

TABLE 2 VERBAL MEMORY TESTS

	M.S.	Discriminant threshold between normals and amnesics	Matched controls' poorest score
Digits forwards	5		
Digits backwards	3		
Logical memory	13.93	15.75	17.06
10-word list mean number of recalled words	7.89	6.58	8.09
10 paired associate learning	5.00	8.73	14.38
Remote memory questionnaire (% correct)	53%	—	58%
Famous name recognition	49	—	55

The maximum score was 56. (3) Learning a 10-word list to the criterion of 2 successful consecutive repetitions with a maximum of 20 trials. The score was the sum of the words correctly recalled over trials divided by the number of trials to criterion or by 20, if the criterion was not reached. (4) Paired associate learning over three trials, with 5 easy and 5 difficult pairs. One point was given to difficult pairs and half a point to easy pairs.

On tests 2, 3 and 4 he scored lower than the poorest matched control. Cut-off scores discriminating normals from amnesics were also available, based on the performance of 100 normal and 20 amnesic patients (De Renzi *et al.*, 1977b). He fell below these cut-off scores on logical memory and paired associate learning, while on the 10-word learning task he scored in the lower range of normality.

Memory for past general events was tested with a questionnaire (Costa *et al.*, 1989) constructed in analogy to those of Albert *et al.* (1979) and Sanders and Warrington (1971) and made up of 8 questions per biennium from 1965 to 1985 with 4 choices per question from which the subject had to choose the correct answer. The test was given to the patient and to matched controls starting with the biennium in which they were 14 yrs old. The patient's percentage correct response was 53% (17/32), while in matched controls the mean was 70% and the poorest score was 58%.

Another test assessed semantic knowledge by requiring the recognition of famous names. Thirty names of famous persons, both contemporary and from the past, were presented written on a card intermingled with 30 unknown names. One point was given for each correct attribution. M.S. scored 49/60. The mean for the matched controls was 56 and the poorest performance 55.

Visual memory (see Table 3)

Memory for visual material was tested with the delayed reproduction of Rey's figure and with face recognition. Rey's figure was copied flawlessly (36/36). Its reproduction after a 20 min filled delay yielded a score of 15 5/36, below the 25th centile, according to the norms provided by Rey (1968) and just below the poorest score found in matched controls.

Face memory was tested with unfamiliar and famous faces. The former test involved first the presentation of 12 displays showing quadruplets of faces that the patient had to rank by age and then the recognition of 48 of these faces when they were paired with a new face. He scored 23/48 (chance level), while the poorest score of matched controls was 40. Famous face recognition was assessed with two tests. One was a familiarity check test in which the patient had to identify the face belonging to a famous person in a display where there were 3 other faces of unknown people. The second test presented 4 famous faces belonging to the same category (e.g., 4 American presidents, 4 Soviet Union leaders, etc.) and asked for the identification of the face named by the examiner. There were 36 items in the familiarity check test and 32 in the identification test and he scored 27 and 26, respectively. In both cases his performance was poorer than the worst score found in matched controls.

TABLE 3 VISUAL MEMORY TESTS

	M.S	Matched controls' worst performance
Rey's figure (20 min delay)	15 5/36	16/36
Unfamiliar face recognition	23/48	40/48
Famous face recognition		
Familiarity	27/36	30/36
Identification	26/32	28/32

Comparison between verbal and visual memory

A direct comparison between verbal and visual memory was performed with two sets of tests. The first involved a recurring stimulus procedure analogous to that proposed by Kimura (1963) which was administered in a verbal and a visual version. Verbal stimuli were 4–6 letter adverbs and prepositions written on a card. Visual stimuli were Vanderplas and Garvin's 6–22 point random shapes. Eight stimuli (either verbal or visual) were shown, each for 3 s, and then presented in succession, intermingled with 12 new stimuli. The entire procedure was repeated twice for a total of 60 presentations, 24 old and 36 new. The score was the number of correct recognitions minus the number of false recognitions. M.S. scored 8/24 on the

verbal test, just below the poorest matched control (10/24), and 20/24 on the visual test, an amazingly good performance at the same level as the matched controls' mean.

The second comparison involved verbal and visual sequential memory. Eight stimuli, either 4–6 letter adverbs and conjunctions or random shapes analogous to those used in the recurring stimulus test, were presented one at a time, each for 3 s. An identical set of stimuli was then laid down on the table in a different order for the patient to arrange them according to the original sequence. Study trials, always presenting the same sequence, and test trials, always presenting a different sequence, alternated until the patient reached a criterion of 2 consecutive, successful reconstructions. Thus in these tests the higher the score, the worse the performance. M.S. scored 32 on the verbal test and 20 on the visual test, while the poorest score of matched controls was 9 and 3, respectively. Thus on both sequential memory tests, he was remarkably impaired.

Spatial memory

The Corsi block tapping test (Milner, 1971) was used to assess spatial span and spatial supraspan learning, following the procedure suggested by De Renzi *et al.* (1977a). Spatial learning was also investigated with a stepping-stone visual map test (De Renzi *et al.*, 1977c). In all these measures M.S. showed no impairment when his performance was compared with that of the normal controls of the above studies (*see* Table 4).

TABLE 4. SPATIAL MEMORY TESTS

	M.S.	Controls' mean
Spatial span ¹	5	5
Supraspan spatial learning ²	4	13
Maze ²	5	13

¹ Number of blocks correctly reproduced, ² trials to criterion. Lower scores correspond to better performance.

DISCUSSION

M.S. showed a normal proficiency on a wide range of mental tasks tapping different cognitive abilities. Attention, oral language, visual perception, visuocognitive praxis, limb and oral praxis and spatial memory were intact and his scores on WAIS and Raven's Progressive Matrices testified that his general intelligence had developed harmoniously and reached a normal level. The outcome of the psychometric investigation substantiated the clinical impression that the difficulties in reading and memory which had been evident from an early age did not arise from mental retardation or emotional problems, but were specific and attributable to the disruption of discrete cerebral mechanisms.

His reading was slow and laborious, especially for nonwords and, although it did not substantially hamper the understanding of the text as shown by his normal performance on the IEA test, it was of sufficient nuisance to prevent him from obtaining pleasure in reading. In writing he made errors that are considered typical of developmental dyslexia, such as mistaking a 'b' for a 'd' or a 'p' for a 'g'. The impairment extended to number reading, especially when they were longer than 3 digits, and it may account for some aspects of his arithmetic disability, which was, however, mainly due to his failure to learn by heart the multiplication tables.

The unique aspect of this patient's symptomatology was his mild to moderate, but consistent, memory impairment. Although the deficit did not have devastating effects observed in global amnesia, it was of sufficient magnitude to create embarrassing problems in daily life and to induce the development of tricks characterizing the behaviour of

amnesic patients. He resorted to tricks employing verbal associations to facilitate the recovery of names, took notes of appointments and errands on a pad, had become particularly adept at guessing from a few hints the missing information. Memory span was not impaired when tested with digits or cubes forwards, but was marginally defective on digits backwards, where he never exceeded a span of 3. On formal testing the long-term deficit was found to involve verbal as well as visual material, and to impair the acquisition of new information and the recall of past events. On practically every test, with the exception of recurring random shapes recognition, his scores fell below the poorest score found in matched controls. Conversely, he performed normally on spatial memory tests, in agreement with the absence of deficit shown in finding his way in familiar environments.

The question may be raised as to whether the memory impairment of this patient may be considered as part of those deficits in areas of behaviour extraneous to reading and writing which have been reported to accompany developmental dyslexia. The only amnesic limitations that have been observed in poor readers and which have been implicated in the defective reading process concern verbal short-term memory (Vellutino, 1979; Shankweiler and Crain, 1986). However, they have not been found to involve visual, nonverbalizable stimuli, such as faces or nonsense shapes (Liberman *et al.*, 1982) and, most of all, to extend to the long-term acquisition of new information, which is the memory performance typically impaired in amnesics and on which our patient consistently failed. It must be added that, to the best of our knowledge, there is no mention in the literature of poor readers with a normal IQ showing memory difficulties in everyday life. We are therefore inclined to see the amnesic problems in this patient as unrelated to the pattern of disabilities reported in developmental dyslexia.

The presence of a memory deficit since childhood makes the present case informative on the dissociation between semantic and episodic memory, namely the preservation of knowledge about the world, concepts, rules and language, independent of a person's identity and past and the loss of memory of personal events that make reference to the spatiotemporal context in which they were experienced (Tulving, 1983). Some authors (Parkin, 1982; Schacter and Tulving, 1982; Wood *et al.*, 1982; Cermak, 1984) consider this dissociation to be characteristic of amnesia in adults, but the evidence adduced in support has been disputed (Baddeley, 1984; Ostergaard, 1987), because semantic memory is based on information learnt at an early age, well before the onset of disease, while episodic memory is tested with material acquired when amnesia is already present. Child amnesia may help to settle the issue. Ostergaard (1987) reported a patient who developed amnesia at the age of 10 yrs and a few years later showed an impairment of semantic as well as episodic memory, thus challenging the likelihood of a dissociation. The pattern of impairment found in the present case is less univocal. His intact language and proficient performance on the Boston Naming test, Peabody test and verbal fluency tests provide clear evidence that the memory deficit has not interfered with the acquisition not only of grammatical and syntactical rules but also of a rich and easily retrievable lexicon, in contrast to the slight anomia that has been observed in poor readers (Denckla and Rudel, 1976; Wolf, 1986). He also has been able to acquire new names that entered linguistic thesaurus only recently, such as AIDS and perestroika. There are, however, other aspects of the semantic domain which exhibit the same degree of impairment as the recall of single episodes: automatized, verbal series (e.g., the months of the year

and the multiplication tables), mathematical rules or algorithms and even the retrieval of proper names have never been learnt with normal proficiency and they indeed represented the main reason for his academic difficulties. It would, therefore, appear that the organization of lexical knowledge into a network of firm semantic relationships, as that provided by language, greatly facilitates its learning and retrieval and gives it a special status in the memory system.

There were no hints in his history or in the neurological and CT scan examination that pointed to a perinatal or postnatal disease or a congenital malformation of the central nervous system as a source of his disability, although the EEG showed slow activity in the left frontotemporal area, possibly indicating a local disturbance of function. The developmental milestones were appropriate: he walked and talked at a normal age and showed good intellectual development apart from his reading and memory impairment. The emotional problems noted by his teachers in the early years of schooling were probably secondary to his learning difficulties, because they were no longer present when he matured and his personal and social adjustment is now excellent. Both the reading and memory impairment have been substantially stable over the years.

Impaired acquisition of reading related to the duration of coma was reported in children who at least 2 yrs before the follow-up examination had sustained skull fracture associated with gross damage to the underlying brain (Shaffer *et al.*, 1980). This is a totally different situation from the mild head trauma, without impairment of consciousness and any neurological sequelae, sustained by our patient at 5 yrs of age, and its relation to his neurobehavioural problems seems, therefore, highly unlikely.

This case enlarges the spectrum of developmental disorders to the area of amnesia. The adjective developmental is used here with the same meaning with which it designates other cognitive disorders that become manifest at an early age, bear no apparent relationship to acquired brain diseases and are explained by assuming a congenital deficiency of the neuronal structures specific for that ability. To the best of our knowledge, no comparable case has ever been reported in the literature, but it is possible that subjects complaining of a nonprogressive memory inadequacy dating back to the early stages of their life do not consider themselves ill and do not seek medical advice.

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MAGNETIC SOURCE LOCALIZATION IN FOCAL EPILEPSY

MULTICHANNEL MAGNETOENCEPHALOGRAPHY CORRELATED WITH MAGNETIC RESONANCE BRAIN IMAGING

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SUMMARY

Initial results of magnetic source localization by means of multichannel recording using a 10 or a 31 channel system are reported. Simultaneous magnetoencephalographic (MEG) and electroencephalographic (EEG) (scalp, sphenoidal and foramen ovale) recording, as well as magnetic resonance imaging (MRI) with a fixed head position, permits the projection of brain structures and the source localized from MEG into a three-dimensional coordinate system. From 8 patients investigated it can be clearly seen that the method is of diagnostic relevance for patients with temporal lobe epilepsy. Results are demonstrated for 3 patients with interesting findings concerning the anatomical correlation with source localization. The findings indicate that MRI-correlated magnetic source localization by means of multichannel recordings provides important advantages in epilepsy research. (1) Increased precision permits noninvasive localization. Deeper sources in the temporal lobe are localized from MEG combined with scalp or minor invasive EEG. (2) Investigation time is considerably shortened. (3) Single events can be localized for supplementary presurgical information concerning the three-dimensional anatomical localization of focal epileptic activity in the brain.

INTRODUCTION

Hypothetical advantages indicate that magnetic field measurements (MEG) are better suited for the localization of epileptic activity than electroencephalographic (EEG) recordings. One reason is that the magnetic field is less influenced by the different conductivities in various brain tissues than the electric field (Cohen and Cuffin, 1983). Another is that MEG recording needs no reference. Pioneer work concerning biomagnetic measurements was performed prior to epileptic research (Williamson and Kaufman, 1981; Romani, 1984). Initial experiences with magnetic field measurements of focal epileptic activity with the application of single channel MEG systems (Barth *et al.*, 1982, 1984; Rose *et al.*, 1987; Sato *et al.*, 1987a; Sutherling *et al.*, 1987; Vieth *et al.*, 1988) and 4 (Ricci *et al.*, 1985) to 7 (Sato *et al.*, 1987b) channels have already shown great promise. The results of computer simulation established that at least 15 recording channels

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are necessary to achieve clinically relevant localization (Abraham-Fuchs *et al.*, 1988). Simultaneous recording of all magnetic channels with a multichannel system offers two advantages: improved accuracy of the results due to coherence without additional processing and considerably shortened investigation time. In the present study, a multichannel recording system was used clinically for the first time in order to investigate the possibility of defining the source three-dimensionally in the brain. Initial comparative observations of sphenoidal EEG (Sp2 = right, Sp1 = left), foramen ovale (FO2 = right, FO1 = left) recordings and multichannel MEG, along with anatomical correlation of the source localization in patients with focal epilepsies, are reported in this contribution.

METHODS

The procedure for the combination of MEG and MRI for magnetic source localization is shown in fig. 1. In the first stage of magnetic source localization, up to 31 channels of MEG were recorded simultaneously with the EEG, displayed on paper and stored in the computer. The simultaneous recording of MEG and EEG included invasive recordings. During synchronous recording of EEG and MEG the head was in a fixed position, as well as during the following MRI measurements. The patient's head was fixed in a reproducible position by means of a silicon impression of the upper teeth which was mounted on a rigid plastic frame (fig. 2). Because of this experimental head fixation technique, MR imaging was performed with the whole-body coil, which accounts for the suboptimal resolution in the MR images. This technique

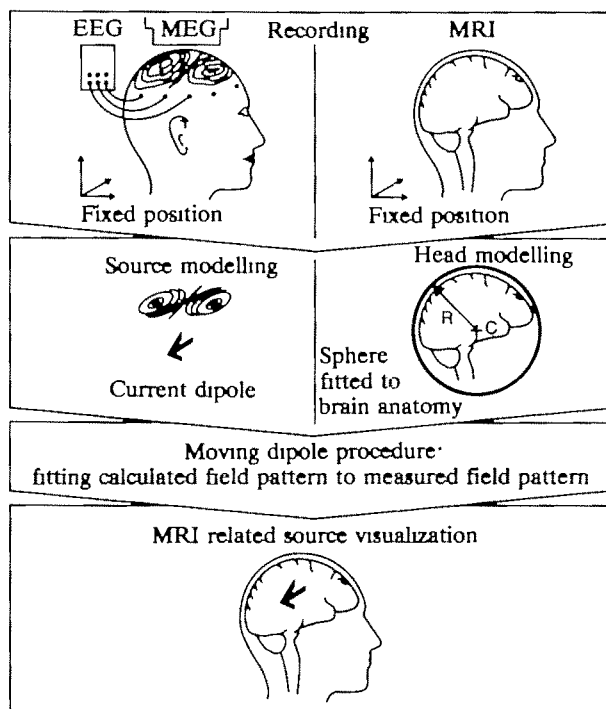


FIG. 1. Flow-chart of MRI-correlated magnetic source localization. Simultaneous recording of MEG/EEG; skull fixed in same coordinate system for MEG/EEG and for MRI; dipole modelling and projection of the magnetic source into the brain.

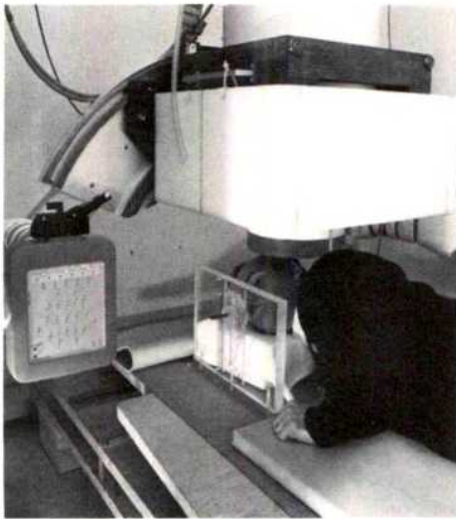


FIG. 2. Arrangement for simultaneous MEG/EEG recording showing the head fixation by means of a silicon bite plate.

permits the projection of brain structures and the source localized from MEG into a three-dimensional coordinate system. The magnetic field distribution was evaluated at the time defined by a spike in the EEG.

System description

An array of 31 first-order gradiometers, sufficiently large so that only one position is required for localization procedures, is combined with a shielded room into a system capable of operating at any time in a hospital environment. The array of 31 axial gradiometers consists of wire coils. Interconnections and feedback transformers are on printed circuit boards. The pick-up loops are 30 mm in diameter. The baseline of the axial gradiometers is 70 mm and the overall diameter of the array of gradiometers is 200 mm. For the arrangement of the gradiometers in an array a planar configuration was chosen. This can be handled relatively easily, both technically and also during measurement and evaluation. The sensor array is placed into a superinsulated fibreglass epoxy Dewar flask (Hoxan Corporation) with a flat bottom and about 25 mm spacing between detection coil and body surface. The Dewar flask has a helium capacity of 25 l, providing cooling for more than 4 days. The Dewar flask and inset are mounted on a stable adjustable support made of nonmagnetic materials. The support allows a vertical shift of 800 mm and can be tilted by $\pm 45^\circ$ in 2 orthogonal directions. Fig. 2 shows the sensor array and the position relative to the head for the measurement of the left hemisphere. The complete detection system is placed inside a shielded room (2 layers of soft magnetic material and 1 aluminium layer, constructed by the Vacuumschmelze Co.), which rests on a concrete foundation. The background DC field and DC field gradient inside the shielded room are reduced by several orders of magnitude relative to the environment, i.e., by a shielding factor of 1000 above 2 Hz. The system allows the simultaneous recording of magnetic MEG/MCG and electric EEG/ECG channels, as well as respiration and control signals. Signals can be displayed by an on-line analog monitor and recorder. After analog to digital conversion the data are preprocessed and stored in a fast computer.

Patients

Eight patients with pharmacoresistant partial epilepsy have been investigated up to now (Table 1). All patients showed focal interictal epileptic activity in the temporal lobe, in MEG as well as in EEG.

The first 3 patients (Cases 1–3, Table 1) have been recorded by means of a 10 channel system. To measure the magnetic field in an area sufficient for localization, the field distribution has been patched from 4 subsequently recorded sensor positions. For evaluation the covariance analysis (Chapman *et al.*, 1983) was used, where the localization of the centre of electric activity is carried through from a field map averaged in time and weighted by the simultaneous recorded EEG. In Case 6, 50 spikes in the MEG (23 channels) were averaged. In Case 7, the field distribution was measured and the source was localized



TABLE COMPARISON OF THE RESULTS OF THE DIFFERENT INVESTIGATIVE TECHNIQUES

Case	EEG Spike Focus	OP ECoG	MRI	SPECT	MEG
1	L inf. med temp	+	Astrocytoma	L inf. med temp	Inf med temp. (hippocampus)
2	R temporal	+	Angioma	R temp	Tissue surrounding angioma
3	R temporal	+	Cyst	R temp	Tissue surrounding cyst + inf. med post + lat temp
4	L inf. med temp	+	Normal	L temp cortex	Temp + insular
5	L inf. med temp	+	L hippocampus (SI)	L temp	Midline region
6	R temp		Normal	R temp PET temp. + insular region	Frontotemp + insular
7	R temp	+	R. sylvian fissure (SI)	R temp	Temp at sylvian fissure
8	R temp	+	Angioma	R temp	Tissue surrounding angioma temp

R = right, L = left, + = ECoG performed, SI = increased signal intensity on MRI, inf. med. temp = inferior medial temporal.

Intraoperative ECoG, performed in 7 cases, was in agreement with the preoperative localization results. In 1 case the focal epileptic activity was localized to the inferior medial temporal area in the region of the hippocampus, in 3 cases in the tissue surrounding an angioma (2, 8) or cyst (3), and in 3 patients the magnetic source localization showed focal activity in the area of the sylvian fissure (4, 6, 7). OP ECoG = intraoperative electrocorticography performed.

on the basis of one sharp wave in the MEG (23 channels); in Case 8, 14 spikes were averaged using 24 MEG recording channels. The results of 3 cases with partial epilepsy are reported in detail, which showed interesting findings for anatomical correlation with source localization. Fluorodeoxyglucose (FDG)-PET scanning was performed in Case 6.

Source localization

For source localization a moving dipole algorithm was used (Cuffin, 1985). This iterative procedure correctly takes into account the position of the plane measurement grid relative to the head and the direction of the measured field components at each sensor position, which deviates slightly from the radial direction. The homogeneous sphere model of the head was defined from multialice MR images of each patient. All patients suffered from pharmacoresistant partial epilepsy with a unilateral focus documented by interictal and ictal EEG recordings (Cases 6, 7, 8, right temporal). MEG/EEG recordings were performed in connection with preoperative diagnosis. Continuous long-term recordings with sphenoidal and foramen ovale recordings over a period of 125 h were carried out.

ILLUSTRATIVE CASE HISTORIES

Comparison of interictal EEG spike (sphenoidal and foramen ovale recordings) and MEG: magnetic source localization at the sylvian fissure

Case 6

A 32-yr-old male presented with idiopathic partial epilepsy, with simple-complex partial seizures and secondary generalized seizures from the age of 16 yrs. MRI demonstrated no lesion. During simple-partial seizures an epigastric aura or rising discomfort thoracic sensation occurred. Other partial seizures consisted of deep inspiration and expiration sometimes accompanied with clonus in the left arm or an M2E motor pattern according to Ajmone Marsan and Ralston (1957). At the age of 27 yrs secondary generalized seizures occurred after the above-mentioned initial symptoms of simple and complex partial seizures as well as predominantly tonic seizures or complex partial seizures with tonic involvement or kicking of both legs.

Interictal comparison of scalp EEG with spike activity in the sphenoidal and foramen ovale electrode (FO₂) recorded by means of a common reference (Goldmann) montage showed a maximum amplitude at the right foramen ovale electrode and in the sphenoidal electrode (fig. 3A). *Ictal* video-EEG recording disclosed the occurrence of initial seizure symptoms 7 s before ictal epileptic activity in the EEG (right foramen ovale and sphenoidal electrodes), indicating that seizure onset was not localized in the inferior

medial temporal region. The MEG shows a spike-wave complex after averaging triggered by a spatiotemporal correlation analysis (fig. 3B). The spatiotemporal correlation algorithm works on the basis of the propagation electrical activity being characterized by a well-defined order of the sequence of magnetic field patterns within the time interval of interest. The time pattern within one MEG or EEG channel is likewise defined by the variation of the location, orientation and strength of the source. Conversely, the characteristic features of a spatial magnetic field pattern are defined only by location and orientation of the source, the source strength being only a scaling factor which does not influence the correlation coefficient of the two subsequent maps. Comparison and recognition of events of excitation is therefore achieved by a combined correlation of temporal and spatial patterns. The MEG map is calculated at the point in time of the maximum for the foramen ovale spike (fig. 4A). The result of magnetic source localization from the spike shows a focus in the right frontotemporal region (fig. 4B, c) in the depths of the sylvian fissure in the insular cortex. The confidence limit of the localized source is marked by a white circular area.

FDG-PET scanning showed hypometabolism in a zone between anterior parts of the hippocampus and temporal pole and also at the insular region. Without averaging, MEG additionally showed interictal rhythmic

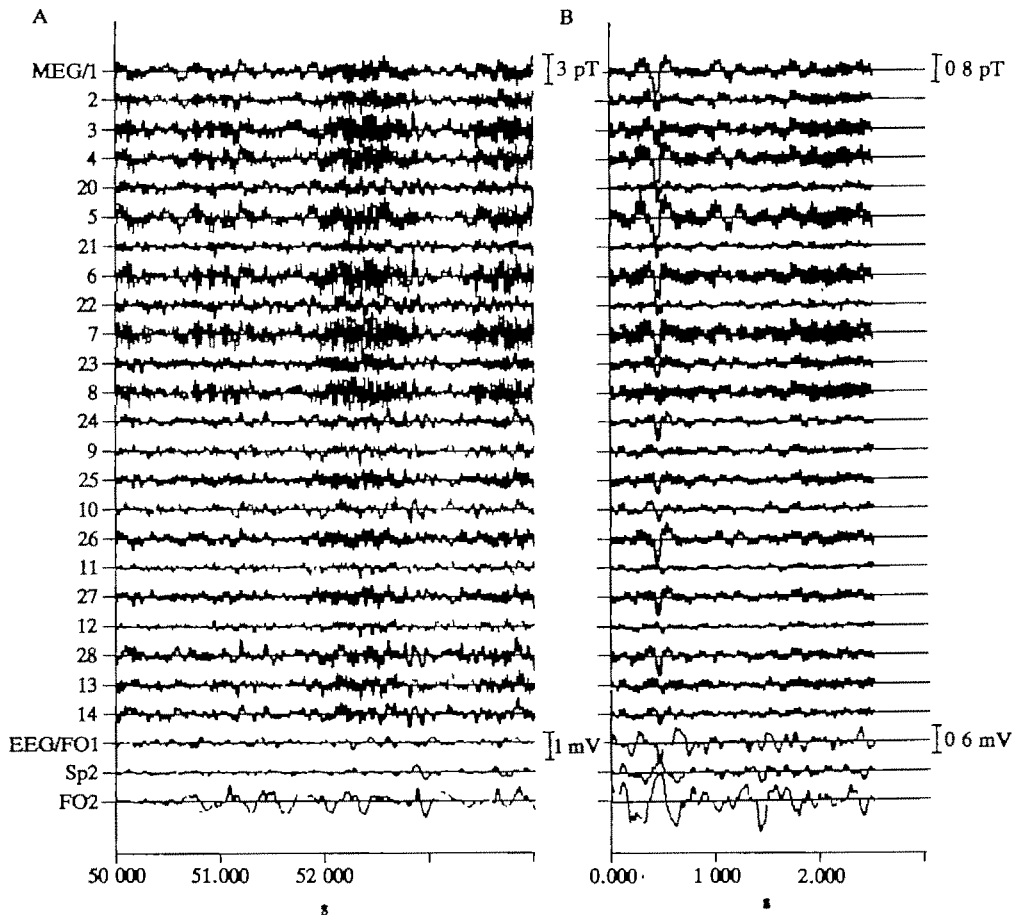


Fig. 3. Case 6. Interictal spike activity in foramen ovale and sphenoidal EEG recordings compared with MEG activity. A, without averaging showing 24 Hz rhythmic MEG activity, B, average of 50 spikes triggered by spatiotemporal correlation analysis spike wave complex in the MEG.

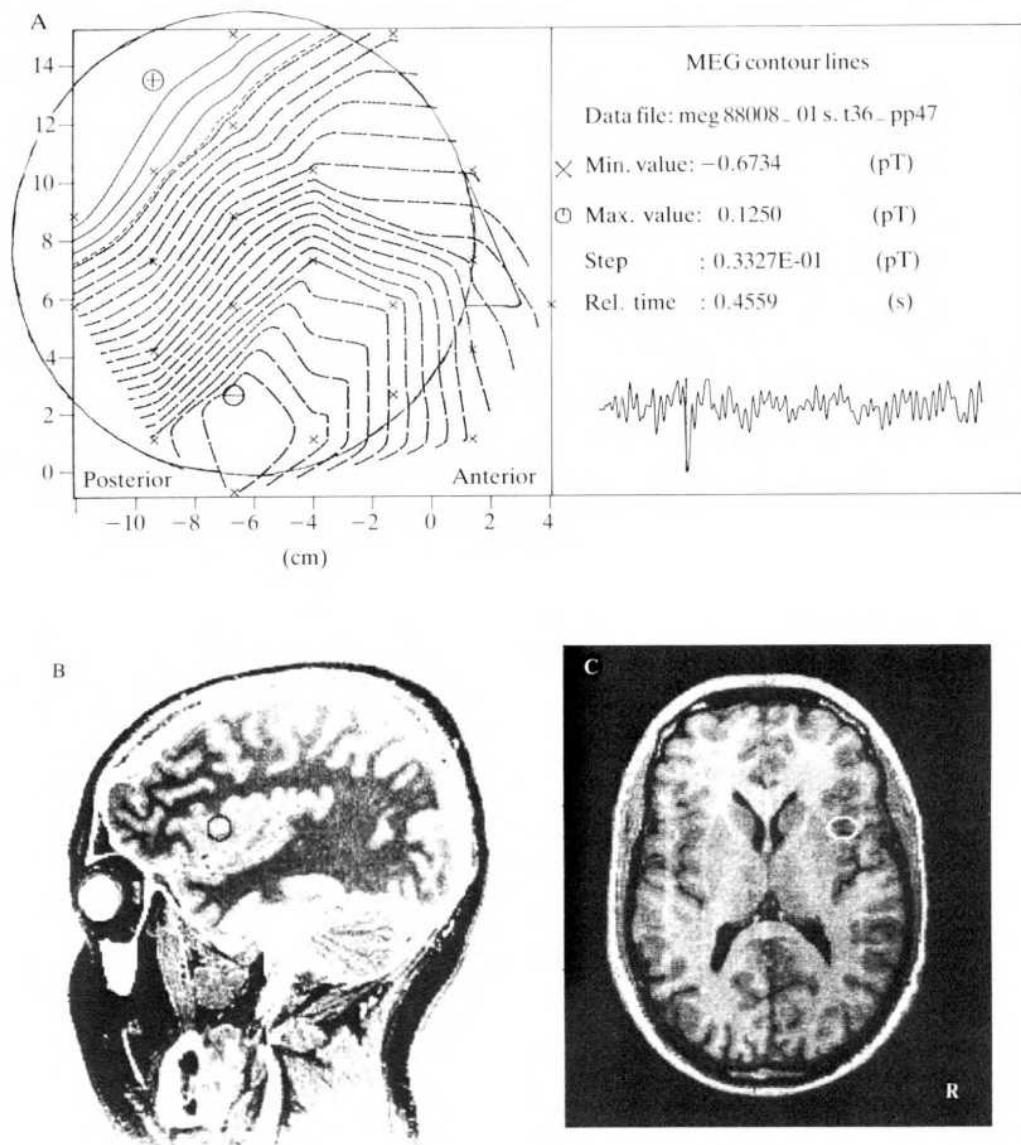


FIG. 4. Case 6. A, MEG isofield map recorded by 31-channel system at the time of the spike maximum after averaging. B, magnetic source localization from the spike correlated with brain imaging; focus in the right insular cortex; MR imaging with head coil; sagittal view. C, axial view.

burst activity of 24 Hz (fig. 3A). This electrical activity which was not visible in the EEG recordings was localized from the MEG at the frontobasal region.

Case 7

A 26-yr-old male patient presented with temporal lobe epilepsy. He had complex partial seizures (3–4 per week) with an epigastric aura, moaning, fixed gaze and gestural automatisms; occasionally secondary

generalized tonic-clonic grand mal seizures. Long-term monitoring with video-EEG revealed interictal right temporal focal epileptic activity, with wide phase reversal in the surface electrodes between F8 and T6, as well as frequent spike activity in the right foramen ovale and sphenoidal electrodes. In complex-partial seizures, initial spike activity in the right foramen ovale electrode was recorded (fig. 5A, B). The magnetic field distribution at the time of a single sharp wave in the scalp (zygomatic electrode) is shown in fig. 6. At the bottom of fig. 6, the signal of the zygomatic electrode is shown, the cursor indicating the time of localization. Only at this instant did the magnetic field distribution have a dipolar pattern. The results of magnetic source localization show a focus located deep in the right temporal area in the region of the sylvian fissure (fig. 7). Surgical treatment was performed 1 yr ago because of pharmacoresistant temporal lobe epilepsy. Intraoperative corticography showed pronounced spike activity in the sylvian region and in a zone corresponding to the medial part of the superior temporal gyrus, and the medial and inferior part of the right temporal lobe. After tailored surgical removal of the amygdalohippocampal complex by means of a transsylvian approach and the spiking neocortical temporal lobe area, it was possible to control the complex-partial and tonic clonic seizures.

Magnetic source localization correlated with an identifiable lesion

Case 8

A 27-yr-old woman had complex partial seizures due to pharmacoresistant temporal lobe epilepsy. MRI showed an angioma in the right temporal region in the posterior part of the inferior and medial temporal gyri. Interictal focal epileptic activity was recorded with maximum amplitude in the inferior medial region (at Sp2 and FO2) and with lesser amplitude at F8, Zy2, T2, T4 and T6. Seizure onset was recorded from the right temporal area, either at the inferior medial (FO2 or Sp2 electrodes) or predominantly in the posterior temporal (T6) and inferior medial (Sp2, FO2) electrodes.

Magnetic source localization showed focal epileptic activity in the brain tissue surrounding the angioma (fig. 8). Electrocorticographic (ECoG) findings were in accordance with the localization from MEG. After temporal lobectomy 6 months ago the patient became seizure free.

RESULTS AND DISCUSSION

The first multichannel recording of the magnetic field over one hemisphere permitted source localization in the temporal lobe. Localization of focal epileptic activity agreed with findings of interictal and ictal video-EEG recording using scalp, sphenoidal and foramen ovale recordings, as well as intraoperative ECoG (Cases 1–3, 5, 7, 8), indicating that the focus is in the temporal lobe. Furthermore in all cases, investigations by means of interictal and ictal ^{99m}Tc -HMPAO SPECT showed abnormalities in the temporal lobe in which the focus was localized. In 3 cases magnetic source localization showed that the focal epileptic activity was found in the depth of the sylvian fissure (Cases 4, 6, 7) in the insular cortex (confirmed by ECoG in Cases 4 and 7, by PET in Case 6).

The comparison of interictal EEG in the sphenoidal and foramen ovale recording with MEG shows rhythmic activity of 24 Hz in the MEG which was not visible in the EEG recordings. It is possible that intracellular epileptiform activities are only demonstrable in MEG recordings. A characteristic of neurons is the tendency to fire in bursts (Calvin *et al.*, 1968, 1973), but beta activity can be also due to antiepileptic medication. Another explanation may be that in patients with partial epilepsies and focal-seizure onset, EEG recordings showed initial flattening or polyspike activity (18–25 Hz). Since the 24 Hz activity recorded by means of MEG in Case 6 is localized to the frontobasal brain region, probably it may be attributable to interictal epileptic activity of the brain, which was recorded at the frontotemporal and insular region in the same patient but also physiological activity (e.g., sleep-induced) has to be considered. Since no final interpretation of this

observation can be given, the phenomenon is only described as regional rhythmic magnetic burst activity.

In this investigation, foramen ovale electrodes were used for the first time for spike identification in MEG. In the second case, 50 spikes were investigated and summarized, and in the third case the noninvasive localization was achieved by the distribution of the magnetic field at the point in time of one sharp wave in the scalp EEG.

The investigation time is substantially shortened by multichannel recording (1 h) and therefore offers considerable additional advantages in comparison with single-channel recordings lasting several hours. In comparison with the usual time-consuming and uncomfortable examinations of the intensive seizure monitoring or single channel MEG

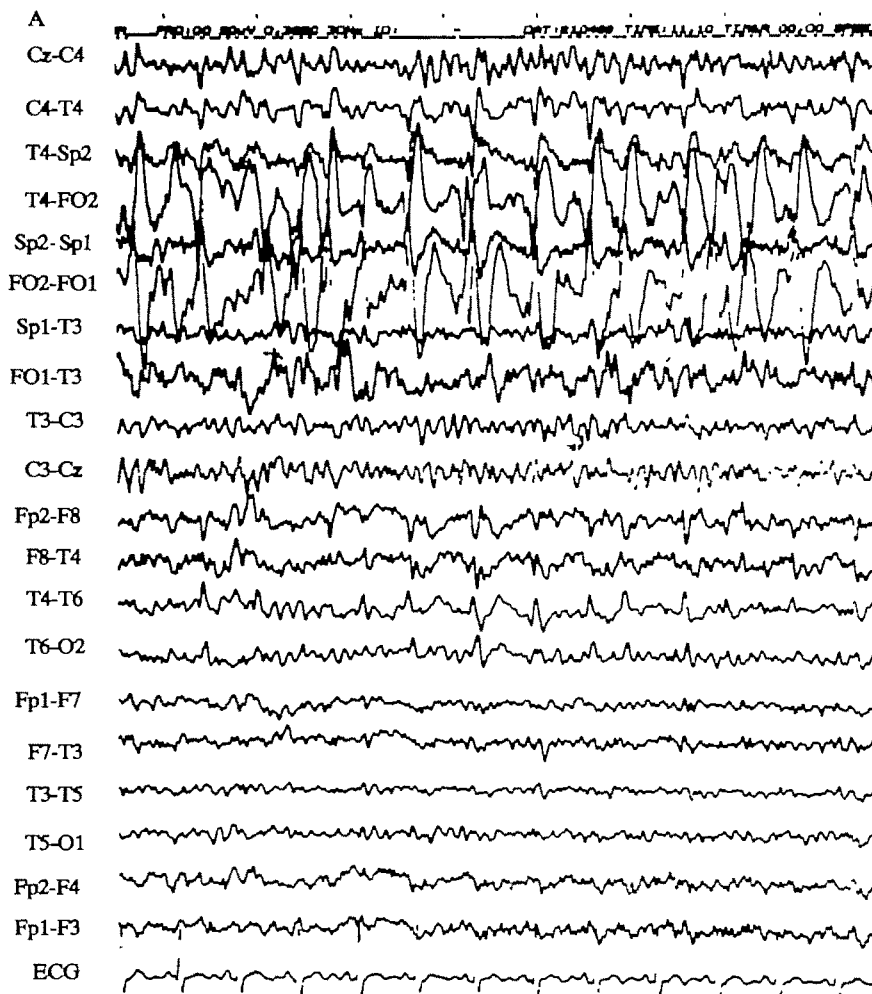


FIG. 5. Case 7. Foramen ovale and sphenoidal activity for the interictal (A) and ictal onset (B, on facing page) of a complex partial seizure. FO2 = foramen ovale recording on right, FO1 on left; Sp2 = sphenoidal electrode recording on right, Sp1 left.

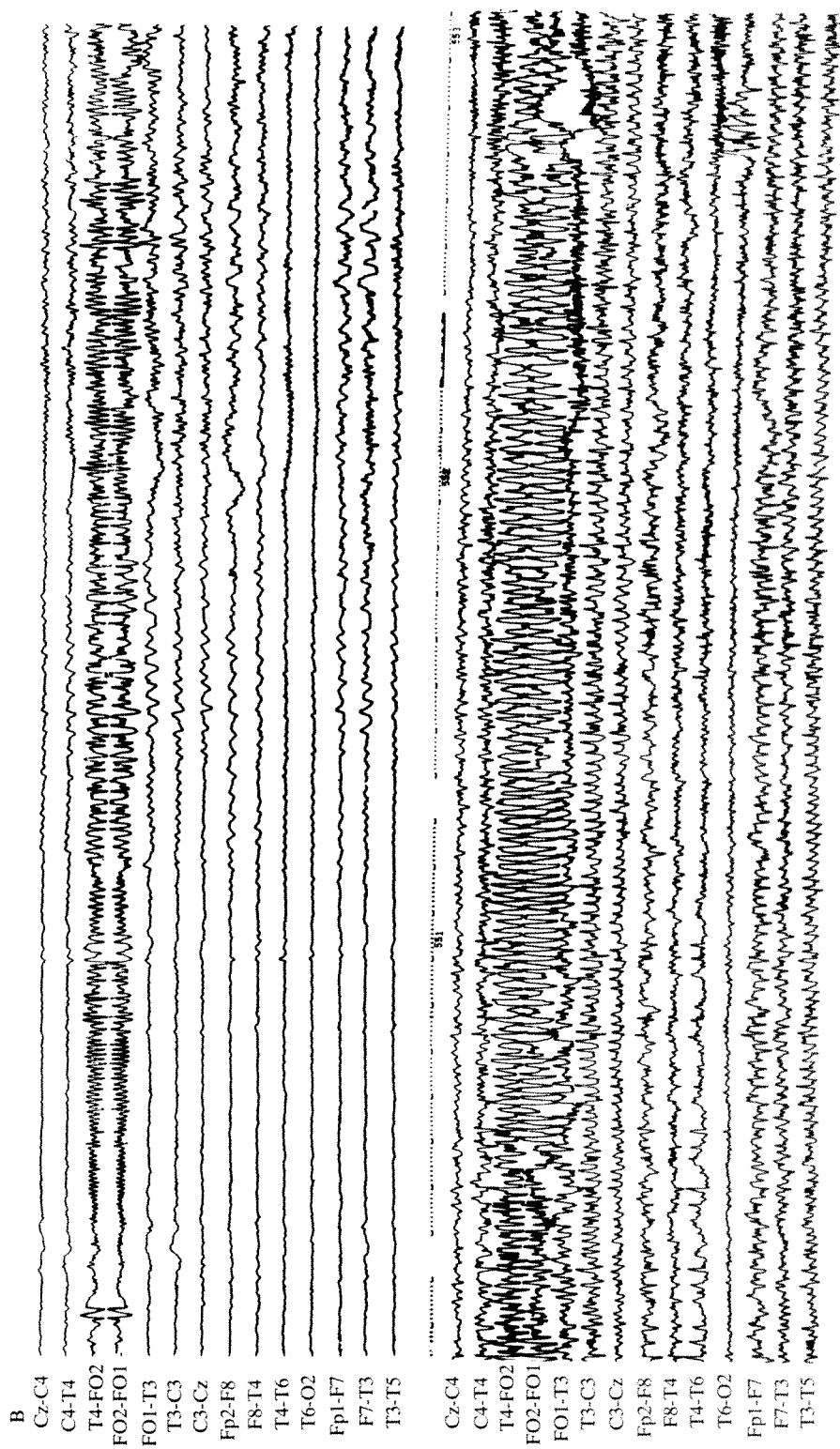


FIG. 5B.

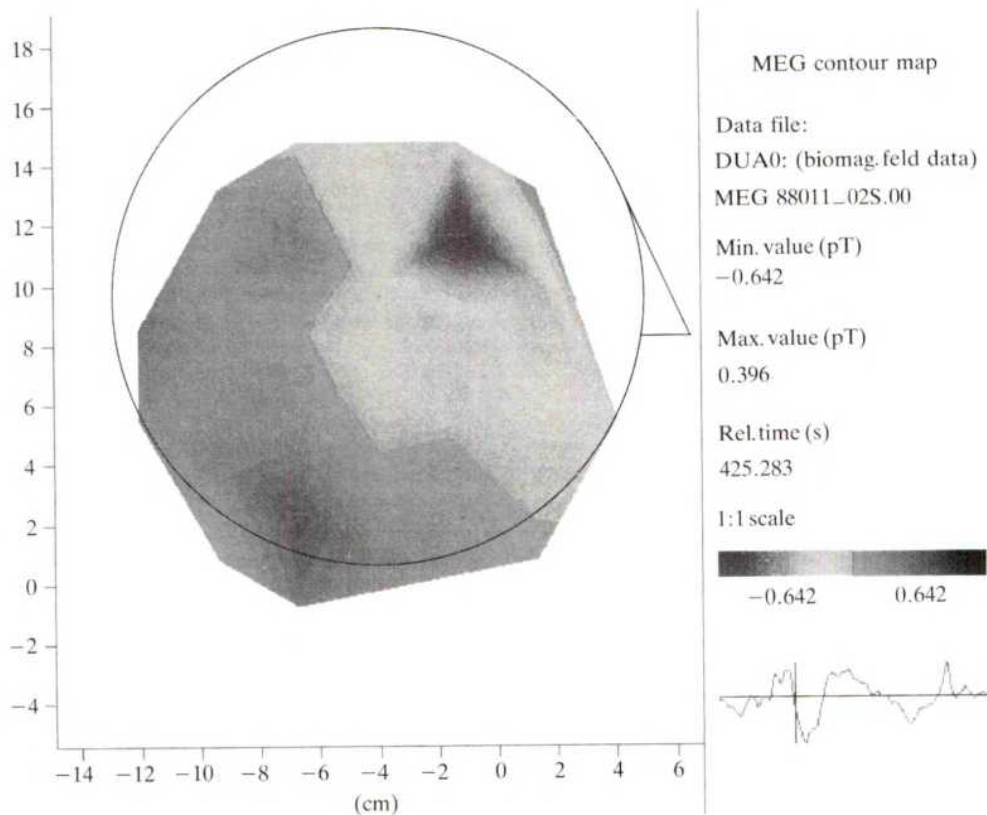


FIG. 6. Case 7. MEG isofield map recorded by 31-channel system; at the bottom right, the time signal from the zygomatic electrode and the moment of mapping are shown.

recording, multichannel MEG recording offers a noninvasive method with short recording times and promising results even for the localization of deeper spikes.

Some papers on the MEG of selected epileptic patients have reported that interictal epileptic spike activity has been clearly visible in the MEG recording. With the 8 cases reported here, spike occurrence could be recognized from the MEG alone only in 2 cases. In the other 6 cases, the occurrence of spikes necessary for the localization was identified by the simultaneous EEG recordings. This is partly due to the fact that in this multichannel system, first order gradiometers with a baseline of 7 cm are used, whereas in most other studies second order gradiometers with a shorter baseline have been employed. This leads to an increased signal from the background brain activity relative to cortical spike signals in the measurements reported here. In addition, we have found that for reliable localization with multichannel systems, the time consuming procedure for exact positioning of the sensors to the field extremes is not necessary.

For inferior medial (e.g., hippocampal) focal epileptic activity (Case 1), foramen ovale EEG spikes or EEG spikes from other electrodes were used to determine the MEG epoch for averaging. The results (Cases 1, 8) showed a close correlation of interictal focal

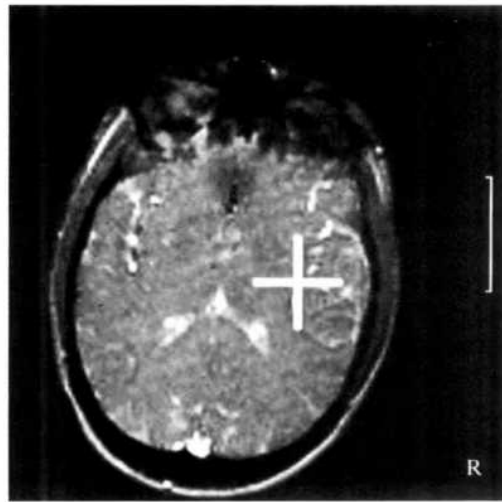


FIG. 7. *Case 7.* Magnetic source localization correlated with brain imaging. There is a deeply located focus in the area of the right sylvian fissure; the cross indicates the confidence limits of localization.

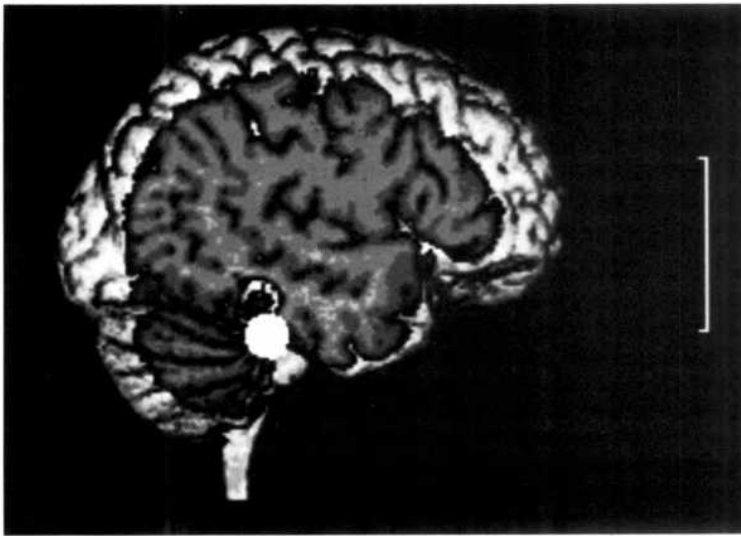


FIG. 8. *Case 8.* Magnetic source localization shows focal epileptic activity in the brain tissue surrounding the angioma. 3D MR imaging with a head coil showing the angioma and a white sphere indicating the confidence limits of the localization.

epileptic activity with brain lesions in superficial and deeper parts of the temporal lobe and demonstrated focal epileptic activity in the insular cortex in the depth of the sylvian fissure (Cases 4, 6, 7) which is difficult to recognize or even 'buried' with respect to localization by means of scalp EEG and even foramen ovale recordings. Although seizures

start in Case 7 at least 50% of the time in the inferior medial temporal regions (foramen ovale electrodes, fig. 5B), magnetic source localization revealed focal interictal epileptic activity in the insular cortex indicating that the primary epileptogenic zone was there. In Case 6, inferior medial temporal regions were involved after onset of seizure symptoms. This fact, the clinical history and the features of the initial simple partial seizure (e.g., forced breathing, thoracic aura, secondary motor involvement such as an M2E pattern, kicking of the legs) and the PET findings suggested an extratemporal origin of focal epileptic activity and reinforced the MEG localization of interictal epileptic activity to the insular region. An operation was performed in 7 patients. In Case 1 only partial removal of the astrocytoma was possible from the hippocampus where the dipolar source was localized. Seizure frequency was only slightly reduced. The other cases were operated on between a half and one and a half years ago and became free both of complex partial and tonic-clonic seizures. The complementary information given by the EEG and MEG explained the intrasulcal localization of a buried EEG focus in the sylvian fissure (Cases 6, 7).

Localization from a single event may be misleading. In Case 8, therefore, magnetic source localization was performed using 3 single spikes and the average of 14 spikes. Both procedures resulted in the same localization in the tissue surrounding the angioma (fig. 8). Although topographically the results of analysis of several spikes were in agreement in Case 8, more patients have to be investigated with several spikes in the future to determine to what extent interictal focal epileptic activity can be correlated with the predominant seizure-generating structure of the epileptogenic brain area. The cases reported were selected to demonstrate the gain in information by using simultaneous MEG/EEG multichannel recordings for functional-anatomical correlation in the brain of patients with partial epilepsies. Magnetic source localization in combination with the demonstration of the brain anatomy by means of MRI can be considered as an efficient supplement to the preoperative diagnosis. Supplementary presurgical information concerning the three-dimensional anatomical localization of focal epileptic activity can be obtained as an addition to scalp EEG and foramen ovale recordings, indicating localization of the primary epileptic zone in the temporal neocortex or in deeper structures of the temporal lobe (e.g., hippocampus) or in the region of the sylvian fissure. The results of magnetic source localization can confirm EEG recordings, improving the correlation of localization of epileptic activity with the brain anatomy. If there is incomplete congruence between EEG and MEG findings, important indications can be obtained for the necessity of further presurgical investigations including PET scanning, SPECT and even intracerebral depth recordings.

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FAMILIAL PAROXYSMAL KINESIGENIC ATAXIA AND CONTINUOUS MYOKYMIA

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SUMMARY

A large family with paroxysmal ataxia and continuous myokymic discharges is described. The disorder is of autosomal dominant inheritance. During attacks coordination of movements and balance are disturbed; often a postural tremor of the head and the hands and fine twitching in some of the facial and hand muscles are present. The attacks usually last a few minutes and may occur several times per day. They first appear in childhood and tend to abate after early adulthood. The attacks are frequently precipitated by kinesigenic stimuli similar to those in paroxysmal kinesigenic choreoathetosis. Their occurrence can be reduced or prevented by carbonic anhydrase inhibitors. Between attacks a slight postural tremor and ataxia was found in a few of the elderly affected members. Fine rippling myokymia was obvious in a few and could be detected on close inspection in about half of the adults. Electromyography (EMG) showed myokymic discharges in all affected members. The characteristics and reactivity of this myokymic activity suggest multiple impulse generation in the peripheral nerves.

INTRODUCTION

Hitherto, 3 families have been described with a remarkable syndrome, combining various expressions of continuous motor unit activity (CMUA) with paroxysms of ataxia and shaking or titubation (Van Dyke *et al.*, 1975; Hanson *et al.*, 1977; Gancher and Nutt, 1986). On the one hand it has been compared with the paroxysmal dyskinesias or classified among the episodic ataxias, on the other hand it has been related to myokymia and neuromyotonia. The uneasy classification of this syndrome may follow from its combination of signs of both central and peripheral nervous origin with prominence of one or the other. The disappearance of the CMUA following curare administration and its persistence during proximal nerve block point to impulse generation in peripheral nerves. The pathogenesis of the attacks of disturbed coordination and jerking has not been demonstrated. We describe a further large family with this syndrome and supply additional information about the characteristics of the CMUA.

CASE DESCRIPTIONS

Fig. 1 shows the pedigree. Of the 24 members alive at the onset of this investigation, 22 have been examined by one of us (E.B.). First hand accounts were obtained of the deceased affected members and of the 2 living affected members who could not be seen by us (IV-24, V-5). In addition, medical records were available for one of these (IV-24). Verbatim histories were completed by a written enquiry. For 3 patients spontaneous and induced attacks were documented on film.

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During this treatment very short or abortive attacks were noticed, consisting of a sudden sensation of stiffness or limpness in his body, not followed by a disturbance of movement. The treatment with sulthiame has been continued for about 1 yr without a clear loss of effectiveness. Side effects caused by sulthiame were paraesthesiae, intermittent stiffness in his hands and fatigue. The paraesthesiae could be reduced by oral potassium chloride suppletion.

Case IV-22

The mother of the proband, was 25 yrs old when examined in 1983. She had been affected by the attacks since the age of 3 yrs. The onset of the attacks was sudden and marked by a 'click' in the head. In a few seconds this was followed by a sensation of heaviness, slowness and weakness, which could start either in her head or in her legs and involved the rest of her body in a matter of seconds. At the end of an attack, this sensation at times remained longer either in her hands or her feet but it always began and ceased symmetrically. Some attacks were accompanied by a feeling of stiffness in her face or hands. Severe attacks were characterized by trembling in the muscles around her eyes and mouth and trembling or shaking of her legs, hands and body. Relaxation could diminish the shaking. Together with this sensation of weakness and with the trembling there was a more or less profound loss of control of directed movements. Her gait was unsteady, sometimes resulting in falls, arm movements were incoordinated and her speech was dysarthric, as if she were drunk or had a swollen tongue. Her eye movements felt impeded; the eyes were staring and her vision was blurred, sometimes with a suggestion of double vision. Vertigo, oscillopsia or autonomic symptoms were absent. Minor attacks often remained unnoticed by others. The attacks usually lasted 0.5–2 min with a range of several seconds to about 10 min. After the onset the intensity increased over 10–20 s and at the termination diminished more gradually. Their frequency varied from once in several weeks to more than 10 in one day and declined after her twentieth year. During her 2 pregnancies, attacks had occurred infrequently. The attacks could occur spontaneously but were usually brought about by an abrupt movement following rest, for instance jumping out of bed, or by a change in speed or direction of a movement involving her body, such as forceful braking while cycling. Attacks occurred more easily when she was startled or nervous. At school she often had attacks during gymnastics when jumping or running and she was teased by her classmates who had discovered that she would have an attack when they chased her. Attacks could be avoided by rising deliberately and slowly from sitting. To shorten an attack she ritually applied cold water to her wrists. She had had several cycle accidents and once nearly drowned because of an attack.

Examination. Eye movements and coordination were normal. There was no nystagmus and no resting or postural tremor. At the initial examination myokymia was not noticed. When special attention was paid to this at a later date myokymia could be observed as fine skin rippling and could be deduced from small irregular finger movements when her hands were held prone and relaxed. The myokymic rippling was enhanced for several minutes following 3 min of forearm ischaemia. At EMG examination myokymic discharges were found in many muscles, including clinically silent ones.

Treatment and follow-up. Drug treatment with clomipramine, 75 mg per day for 3 wks, and phenytoin 200 mg per day for 1 month, had no clear effect. Sulthiame has been effective and has been continued with some interruptions for 2 yrs, at a dose of 50–200 mg daily. During this treatment, abortive attacks were still noticed rather frequently, lasting only a few seconds and consisted of the characteristic sensation without the ensuing ataxia. Troublesome side effects were paraesthesiae and intermittent carpal spasm.

Case III-25

A 59-yr-old woman when examined in 1983. She suffered attacks from the age of 7 yrs. The frequency was highest at about the age of 50 yrs, following hysterectomy. Since then, the attack rate had fallen from once a month to about once in 3 months. Attacks were either short, lasting about 15 min, or prolonged, persisting for 5–7 h. The onset was marked by a shock-like sensation in her head, followed by a limp, stiff or trembling sensation which spread to her arms and legs. The persistence of this feeling in her legs after 15 min usually indicated a prolonged attack. During an attack her movements were hampered and imprecise, her gait was staggering and her speech was slurred. Often there was tremor of her head and sometimes her vision was blurred. Vertigo or nausea never occurred. She had noticed that sometimes her hands were somewhat bluish and swollen before an attack and slender and white afterwards. During a

prolonged attack her mouth became dry and following an attack she noticed urinary frequency. She found that the best way to cope with an attack was to avoid movements and to sleep; after a few hours of sleep a long attack had usually terminated.

The attacks could occur spontaneously but were also brought about by movement. Occasionally an attack occurred at night and was noticed when she awoke. At a young age most of the attacks happened at weekends and when relaxing. She felt that activity to some extent prevented the attacks. Susceptibility seemed to be increased during illness, during seasonal changes and when she felt tired or stressed. Prevention was usually sought by thoughtful, slow execution of movements. In a waiting room she would, for instance, choose a place where she would not have to turn around when called.

Examination. There was no tremor or nystagmus and coordination was normal. Rippling of the skin was visible in the small hand muscles, and at subsequent visits sometimes noticed in her forearms and around her mouth and eyes. In her face the rippling was reminiscent of 'live flesh' and in the larger muscles it was comparable to benign fasciculation. Apparently due to myokymia, the thumbs were held slightly in adduction-opposition. On EMG, myokymic activity was found in face, arms and legs, most pronounced in the distal parts.

Witnessed attack. On one occasion, we had the opportunity of examining her at home during a prolonged attack. She had alerted us when the 'limp-stiff' feeling in her legs persisted and we arrived about 1 h after the onset. From the onset the intensity had fluctuated without symptom-free intervals. Speaking and movement caused an increase of the symptoms. The myokymia was not obviously increased. Respiration was somewhat deepened and her speech was slow and a little hesitant. Her gait was broad-based with short unequal steps and was performed in a slow rhythm. Tandem walking was impossible. Performance of alternating movements with her tongue, hands and feet was slow and imprecise. The heel/shin test showed moderate ataxia and the finger/nose test was performed slowly. The recoil sign of Gordon Holmes and hypermetria were absent. Tendon reflexes and resistance to passive movement were normal. There was no nystagmus. When searching in her handbag for tablets, her movements were clumsy and imprecise, discrete finger movements being poor. There was a marked 3–4 Hz rotatory postural tremor of the head and a fine postural tremor of the hands, both disappearing on complete relaxation.

Treatment and follow-up. Two carbonic anhydrase inhibiting drugs have been tried to prevent attacks: acetazolamide 250–500 mg daily and diclofenamide 50 mg per day. Paraesthesiae and stiffening of the hands caused both drugs to be stopped after a few days; 200 mg sulthiame, taken once during a long attack, appeared to shorten the attack but caused paraesthesiae which lasted 1 wk. During a short course of phenytoin, with a blood level of 5.5 µg one attack occurred which she felt was milder than usual; her speech was not slurred, the tremor was absent and she was able to walk reasonably well.

RESULTS

From the different case histories the following pattern of attacks emerges (*see* Appendix 1). The attacks usually commence between the fifth and seventh years of life. The onset is sudden and, in about half of the patients, marked by a click or shock. Within a few seconds this is followed by a diffuse evolving or spreading sensation of stiffness or limpness, causing awareness of an attack without the occurrence of actual movement. The intensity peaks in a matter of seconds and subsequently declines gradually over several minutes. In addition to the characteristic incoordination, most patients notice trembling of the face, head or limbs and many report visual blurring and staring of the eyes. A minority report a feeling of warmth or increased perspiration. Nausea or rotatory vertigo and involuntary jerking or writhing movements are absent. The 3 patients who also suffer from epilepsy easily discriminate the two kinds of attack. Attacks vary in severity and duration and may pass unnoticed when minor. During an attack most patients stand still or sit down but some can continue walking. Writing or eating is usually

impossible. When an attack occurs while cycling most patients dismount quickly; some are unable to do so and have to fall in order to prevent an accident.

The duration of the attacks is usually between a few seconds and about 10 min, extending up to 6 h in a few individuals. The attacks tend to be shorter in childhood. An attack is rarely repeated within 1 h (III-34). The frequency tends to be highest in the first and second decades and shows a rather large variation within and between individuals, ranging from more than 15 a day to less than 1 per month. Some of the elderly patients have attacks as infrequently as once every 2 or 3 yrs.

Attacks can occur spontaneously but are usually brought on by a sudden or unexpected movement. Typical examples mentioned are rising from a chair, getting up and subsequently descending from a bus, performing gymnastics or sport, running, sliding, turning, dancing and sitting in a roundabout. Anxiety and startle enhance the susceptibility, for example as may happen when appearing in front of the class at school, when getting up to answer the telephone or to enter a doctor's office. During illness, attacks occur more often; one boy (V-12) for many years had attacks exclusively during intercurrent infections. Fatigue and emotional upset are regarded as additional risk factors by half of the patients. Hunger, lack of sleep or the use of alcohol do not enhance the susceptibility. During pregnancy the frequency is often reduced, while an increase premenstrually was mentioned by 3 patients (IV-15, IV-17, V-3). As can be understood, prevention of attacks is in the first place attempted by avoidance of gymnastics, sport and sudden movements. One patient for instance used to wait standing next to the physician's door. Alleviation or shortening of an attack is sought by sitting or lying down and by avoidance of movement. Habitually several patients apply a cold flannel to their face or hands or keep their hands in cold running water. Patients suffering from prolonged attacks try to sleep.

Examination and witnessed attacks

Clinical neurological data during symptom-free periods and during attacks are presented in Appendix 2. The loss of coordination observed in about half of the elderly patients was slight to moderate with an intention tremor in the finger/nose test in 2 of them. The postural tremor of the head or outstretched hands found in a minority of the elderly patients was subtle and the slight resting tremor of the hands was seen in the patient with the most pronounced myokymia (III-33). Nystagmus was occasionally observed in 1 patient only, who was on anticonvulsants (III-26).

Myokymia was obvious in the hands in 4 elderly patients only. However, on careful inspection about half of the patients showed more or less constant fine skin rippling and in another quarter, myokymia could be deduced from minute lateral finger movements, with the hand held in a relaxed prone position. Most of the patients had not previously noticed the muscular twitching, but the peculiar position of the thumb was known to some and referred to as 'vicar's hands'.

We witnessed 14 attacks occurring in 9 patients. In addition, a neurological description was available for 1 patient of what probably was a prolonged attack (IV-9). Eight attacks were purposely provoked, 4 occurred on entering the office and 2 began spontaneously. As a provocation we asked the patients to rise quickly after a loud handclap, sometimes followed by turning around or by hopping, or to run up a staircase quickly. Only a minority of the attempts was successful. The disturbance of coordination and the tremor

started a few seconds after the provocation, reaching a peak after 20–30 s and declining gradually over several minutes. Renewed provocation could enhance a minor attack shortly after its onset but remained ineffective once the attack had terminated.

All attacks were characterized by ataxia with a broad-based gait, a disturbance of limb coordination and a reduced speed of alternating movements. Usually tandem walking and balancing on one leg were impossible. Often a more or less pronounced postural tremor of the arms and head was present and in one instance a tremor of the head was combined with a subtle lateral tremor of the mandible (III-9). Dysarthria, noticed in the majority of the attacks, was characterized by a reduced word fluency and an obstructed rather than a hypotonic speech. In about half of the witnessed attacks myokymia appeared to be increased, mainly in the face, and in 1 case the adduction-opposition position of the thumb was more pronounced. Hyperreflexia with flexor plantar reflexes was found in 2 patients. Nystagmus, athetosis, dystonia or chorea were absent and there was no deficit of muscle power.

Investigations (see Appendix 3)

Three of the 4 abnormal EEGs were compatible with the clinical diagnosis of epilepsy (III-26, IV-13, IV-24). In the 1 case without epilepsy, the EEG showed paroxysmal events. Contingent negative variation in 4 patients was recorded using the S1-S2 paradigm. A normal CT brain scan was obtained in the patient with the most marked interval ataxia and tremor (III-33). An MRI brain scan was performed in the oldest affected family member (III-29), with special attention being paid to the cerebellar vermis; this showed no abnormality. A postmortem examination was performed in 1 patient (III-29) who died from a pontine haemorrhage. Examination of the brain and biopsies of a femoral nerve and an extensor digitorum brevis muscle showed no abnormalities.

Electromyography

Nineteen affected and 3 healthy members have been examined electromyographically, using both concentric needle and surface electrodes. The 3 healthy subjects showed no resting EMG activity. In contrast, spontaneously occurring motor unit activity, ranging from single units to an intermediate interference pattern, was present in all affected members. It was found most easily in hand muscles, but at times also in proximal limb muscles and occasionally in the face. Spontaneous motor unit activity was often encountered in muscles that lacked visible myokymia. Most discharges were regularly repeated duplets or triplets but singlets and multiplets were also seen frequently (fig. 2). In addition to rhythmic activity, more or less irregularly repeated single or grouped potentials occurred.

When occurring rhythmically, the discharges showed a constant rate and independence of the firing of other discharges recorded at the same site. The basic ('burst') discharge frequency varied between 0.5 and 8 Hz and was often in the range of 2–5 Hz. A compensatory increase in burst interval could sometimes be seen in complexes with a variable number of spikes. The length of the series built out of these rhythmic discharges varied from a few seconds to many hours, outlasting the period of examination. Sometimes identical activity was found in the same place following an interval of several weeks. The amplitude of the spontaneously occurring potentials seemed relatively small, about 100–500 μ V on needle electrode recording. The duration of the bursts ranged from

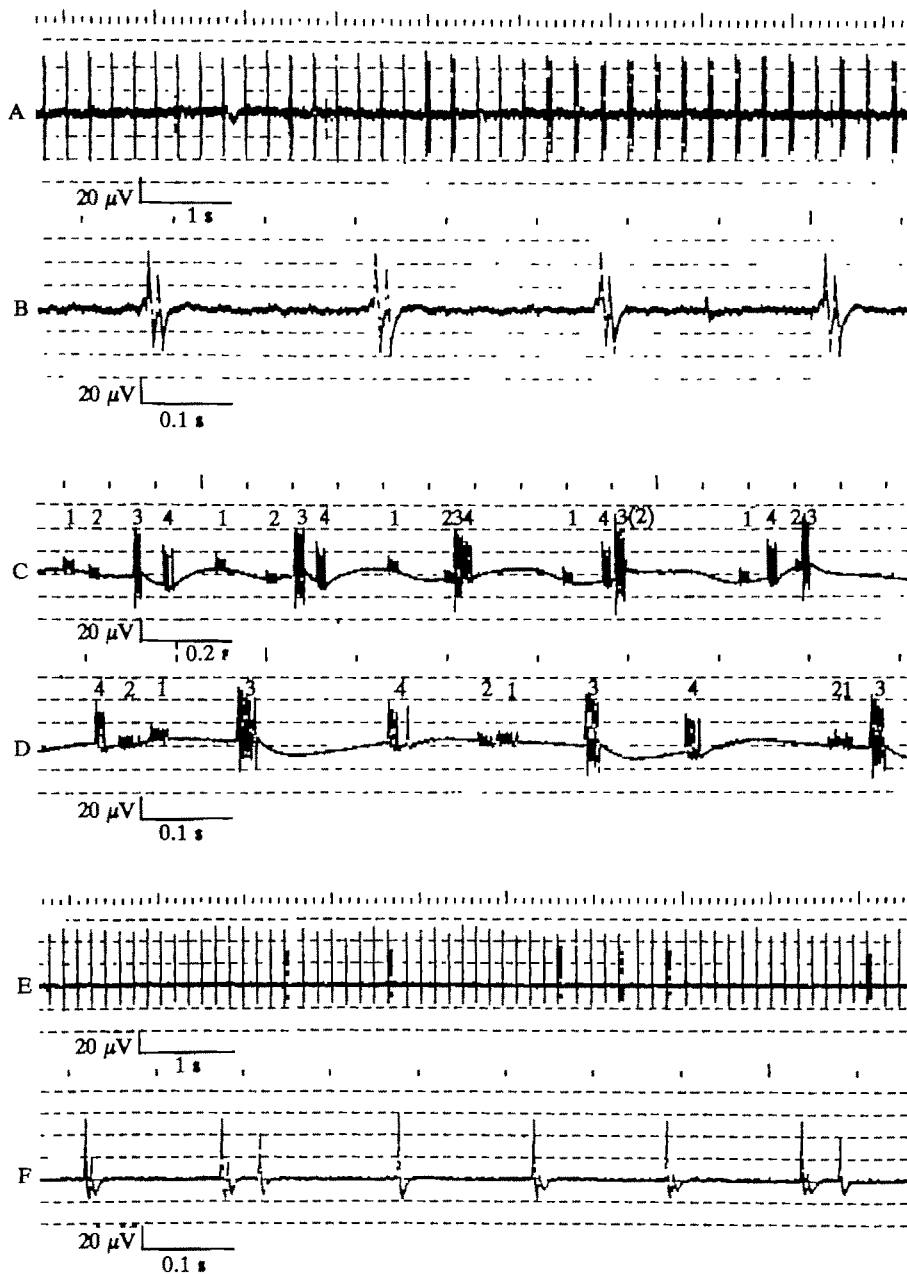


FIG. 2 Spontaneous muscle activity. A, B, rhythmically occurring duplet with some variation in spike interval. *Case III-35*, surface recording from 1st dorsal interosseous muscle of hand. C, D, 4 different multiplets occurring rhythmically and independently of each other with variation in number of spikes (3,4). *Case IV-17*, surface recording from 1st dorsal interosseous muscle during an attack. E, F, rhythmically occurring singlets or sometimes doublets with burst intervals dependent on the number of spikes. A shadow potential is variably present following the first spike. *Case III-24*, 1st dorsal interosseous muscle (concentric needle electrode).

about 5 ms for singlets to more than 25 ms for multiplets. Within the bursts, the spike frequency ranged between 20 and 250 Hz, the lower frequencies occurring in extended duplets. The shape of the separate spikes were usually biphasic or triphasic. True polyphasic spike potentials were not recorded but sometimes the bursts consisted of irregular nonidentical potentials. In some duplets and multiplets, variably present small 'shadow' potentials could be recognized following a larger, normal spike (fig. 3A). Another possibility for dissimilarity of repetitive complexes was a variation in amplitude of one of the spikes (fig. 3B). In addition to spontaneous occurrence, duplets and multiplets were occasionally recruited during voluntary contraction.

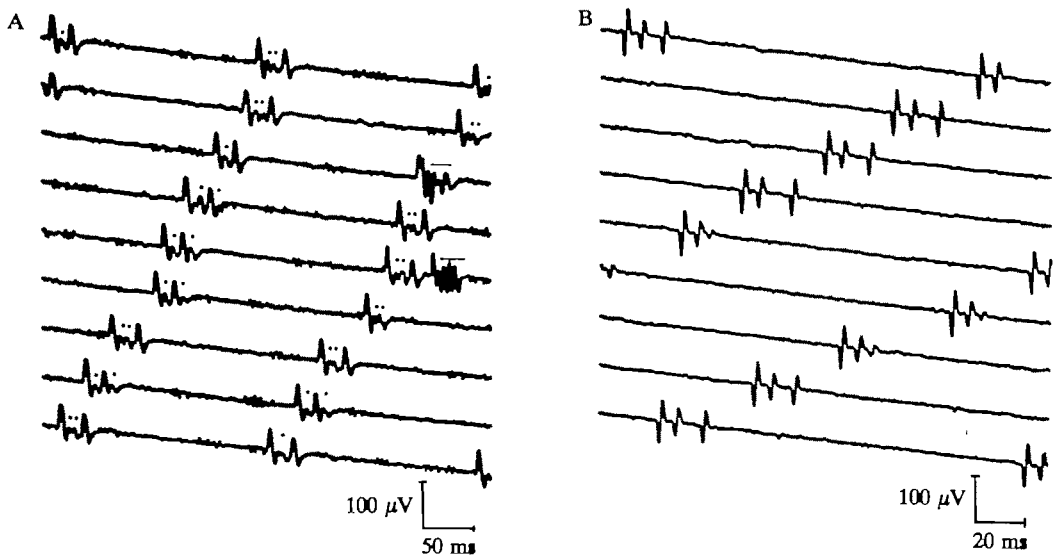


FIG. 3. Burst complex variability. A, rhythmically occurring complex of duplets or sometimes singlets with some variation in spike interval. Shadow potentials () follow the first and sometimes the second spike. Multiplets (—) occur irregularly. Case IV-22, surface recording from abductor pollicis brevis following ischaemia. B, rhythmically discharging triplet with variation in second spike interval. The amplitude of the third spike correlates with the length of the second spike interval. Case V-1, surface recording from abductor digiti minimi.

Reactivity of the spontaneous (myokymic) muscle activity

The resting activity was not inhibited by antagonist contraction but could be suppressed for 5–20 s by a short volitional contraction of the same muscle. Supramaximal nerve stimulation partially suppressed the activity for 100–200 ms. The spontaneous activity in a hand muscle could be increased by heating and decreased by cooling the forearm, with a slight reduction of the burst frequency.

The intravenous administration of 1 g of ionized calcium, investigated in 2 patients, produced a slight to moderate diminution of resting activity and reduced the post-ischaemic recruitment. Hyperventilation caused a moderate rise in burst frequency and less consistently an increase in the number of spikes per burst and recruitment of new bursts.

In 2 patients, spontaneous activity in the hypotenar muscle disappeared completely

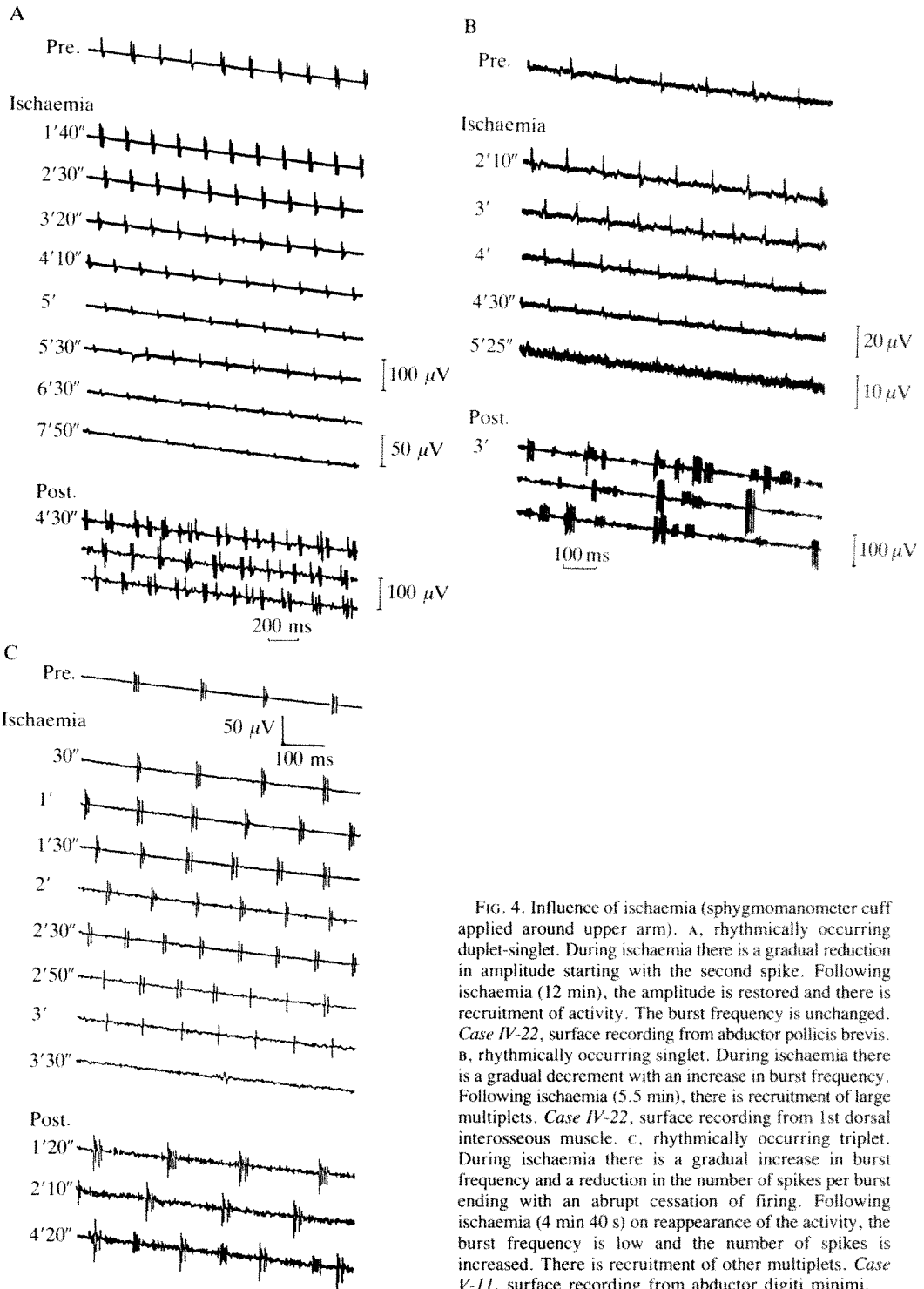


FIG. 4. Influence of ischaemia (sphygmomanometer cuff applied around upper arm). A, rhythmically occurring duplet-singlet. During ischaemia there is a gradual reduction in amplitude starting with the second spike. Following ischaemia (12 min), the amplitude is restored and there is recruitment of activity. The burst frequency is unchanged. *Case IV-22*, surface recording from abductor pollicis brevis. B, rhythmically occurring singlet. During ischaemia there is a gradual decrement with an increase in burst frequency. Following ischaemia (5.5 min), there is recruitment of large multiplets. *Case IV-22*, surface recording from 1st dorsal interosseous muscle. C, rhythmically occurring triplet. During ischaemia there is a gradual increase in burst frequency and a reduction in the number of spikes per burst ending with an abrupt cessation of firing. Following ischaemia (4 min 40 s) on reappearance of the activity, the burst frequency is low and the number of spikes is increased. There is recruitment of other multiplets. *Case V-11*, surface recording from abductor digiti minimi.

when the ulnar nerve was blocked by local anaesthetic at the wrist while only about half of the discharges were abolished by anaesthesia at the level of the elbow.

During treatment with acetazolamide and sulthiame, the myokymic activity was enhanced both by enlargement of existing complexes and by recruitment of new ones.

Using an inflated sphygmomanometer, in 14 patients the influence of limb ischaemia for up to 15 min was investigated (fig. 4). After 5–10 min of ischaemia, the spontaneous discharges disappeared, either with a gradual decay in amplitude or more suddenly with an interruption of their rhythmic occurrence. Sometimes an increase of spontaneous activity was observed during the first few minutes of ischaemia, in 1 instance accompanied by a positive Trousseau sign. In some discharges we found a remarkable rise in the burst frequency to about 2–2.5 times its original level after 0.5–2 min of ischaemia. About a quarter of the complexes recorded from hand muscles showed this reaction when the cuff was applied around the upper arm. When the cuff was applied around the forearm, about 1 in 10–20 complexes reacted in this way. This reaction persisted when repeated up to 6 times and for a certain complex under identical circumstances, it remained unchanged even after an interval of several weeks. Some complexes showed a rise in frequency during ischaemia at the upper arm level but not when the cuff was inflated around the forearm (fig. 5). When a rise in burst frequency occurred during ischaemia, after release of the cuff the frequency fell sharply, sometimes with a temporary disappearance of the discharge, followed by a more gradual rise to the preischaemic level. On the other hand, when the burst frequency was unaltered during ischaemia, it would remain so after reversal of the ischaemia.

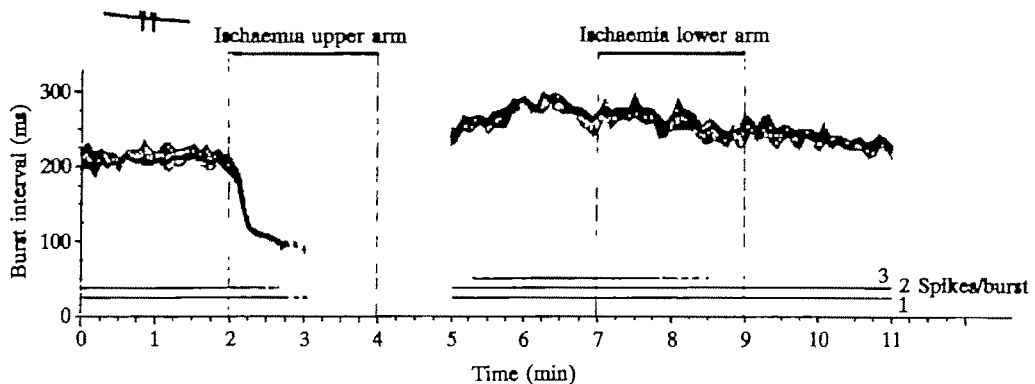


FIG. 5. Influence of ischaemia. Different reaction following upper and lower arm application of the sphygmomanometer cuff. Rhythmically occurring duplet, burst interval plotted against time. Hatched area indicates absolute values; drawn line indicates mean values. Case V-15, surface recording from abductor digiti minimi.

Depending on its duration, ischaemia was followed by a smaller or larger temporary increase of spontaneous activity. This increase was due to recruitment of new, sometimes large, complexes and to enlargement of preexisting complexes with extra spikes (fig. 4). This excess of activity began 0.5–1 min after reversal of ischaemia, reached a maximum at 2–5 min and gradually declined over 10–15 min.

Motor and sensory nerve conduction velocities and distal motor latencies were normal. The muscle fibre conduction velocity, measured with surface electrodes at the biceps brachii muscle in 1 patient, was also normal. Comparing the stimulus thresholds of rectangular and triangular pulses, a normal nerve accommodation was found in 2 patients. When the compound muscle action potential (CMAP) was recorded with surface electrodes from the thenar or hypothenar eminences following supramaximal stimulation at the wrist, in about half of the experiments the CMAP was followed by a small potential with an amplitude of about a third or less of the CMAP amplitude (fig. 6). This afterpotential was suppressed during ischaemia and repetitive following ischaemia. Using twin stimuli with a variable interval between 5 and 500 ms, a comparable recovery cycle of this afterpotential was found in 4 patients (fig. 7). It was suppressed at stimulus intervals up to 30 ms, recovered at intervals between 30 and 60 ms and showed an

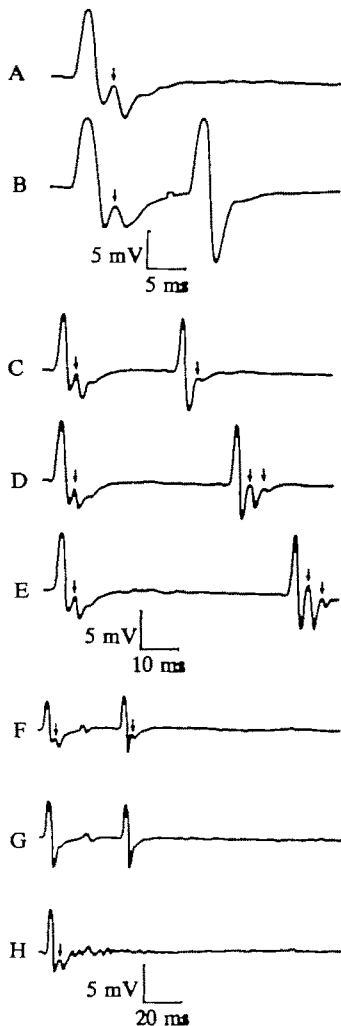


FIG. 6. Nerve stimulation with influence of ischaemia. The compound muscle action potential is followed by an afterpotential (arrow). A, single stimulus. B-E, double stimulation with increasing interval. Case IV-17, supramaximal stimulation of the median nerve at the wrist, surface recording from abductor pollicis brevis. F, double stimulation with 50 ms interval. G, same during 3 min of ischaemia. H, single stimulation following ischaemia. Case III-25, identical recording conditions.

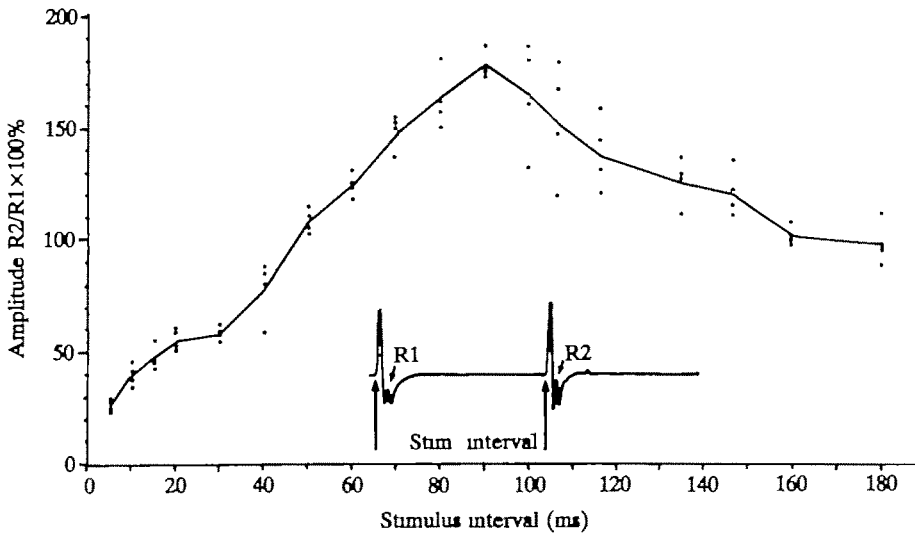


FIG 7 Recovery cycle of afterpotential. The ratio of the amplitudes of the second (R2) and the first (R1) afterpotentials is plotted against the stimulation interval (5–180 ms). The drawn line is the average of 4 measurements. Note 'overshoot' at stimulation intervals between 50 and 160 ms, with a peak of approximately 175% at 90–100 ms. Case IV-22 same recording conditions as in fig. 6.

amplitude 'overshoot' at intervals between 60 and 150 ms with a peak near the 100 ms interval. At this peak, the amplitude of the second afterpotential was 1.5–2 times the amplitude of the first afterpotential.

Therapy

Various drugs have been tried in an attempt to prevent attacks of ataxia in this family (Appendix 3). Phenobarbitone and carbamazepine were ineffective. In 1 patient (IV-24), phenobarbitone effectively prevented epileptic seizures while the attacks of ataxia continued. Phenytoin in a daily dose of 200–325 mg had little or no effect upon the attack frequency. Betahistine, cinnarizine, flunarizine, clomipramine and clonazepam, given to a few patients, did not clearly prevent attacks.

Acetazolamide, initially tried in analogy with its effect in familial periodic ataxia (Griggs *et al.*, 1978), has been used by 12 patients in dosages ranging from 62 to 750 mg per day. In 3 patients who stopped this medication within 1 month because of side effects, the effect could not be evaluated. In the others it has been continued for 2–52 months with a mean of 18 months; in 1 patient it had no clear effect, 4 showed a reduction of the attack rate by more than 50% and 4 were almost free of attacks (less than 1 attack per month). The suppressive effect of acetazolamide started within 2 days and continued for 1–3 days after cessation. Sometimes a remarkable lasting improvement followed prolonged treatment with this drug. Both the suppressive effect and the side effects were dose related. The latter consisted of paraesthesiae, muscle stiffening and easy fatigability and could be partly reduced by potassium chloride supplementation. Of the other carbonic anhydrase inhibiting drugs, diclophenamide caused even stronger side effects and could not be evaluated. Sulthiame, a drug that has also been used successfully in familial periodic

ataxia (Wolf, 1980), caused less side effects and became the preferred drug in most patients. Twelve of them have used this drug in dosages between 50 and 300 mg daily. The effectiveness equalled that of acetazolamide and showed little or no reduction when it was used for more than 3 years. Some patients developed the habit of using the drug only occasionally, for example, a few hours before sporting activities.

DISCUSSION

The mode of inheritance of the trait in this family is autosomal dominant. Excluding a twin who died in infancy, of the 56 members at risk of inheriting the trait, 27 were affected, indicating a relative risk of 48%. As might be expected in a large family, the attacks showed some interindividual variation with regard to symptoms, duration and intensity. Between the attacks minor signs of ataxia and postural tremor were present in some of the older members. Myokymia, which was present in all affected members on EMG, varied in its clinical expression from invisible to skin rippling and an increased opposition of the thumb.

In Appendix 4, data from the 3 previously described families with myokymia and paroxysmal ataxia (HMPA) and of the family described by us are summarized. The age of onset, frequency, duration and kinesigenic provocation of the attacks of ataxia seem to a large extent comparable. The presence of jerking during the attacks and the intensity of myokymia both during and between the attacks may indicate quantitative differences. Other differences are suggested with regard to the presence of contractures in early life and the reaction to phenytoin and possibly also to acetazolamide both for the attacks of ataxia and the myokymia. The results of muscle and nerve biopsies show divergence.

In other families with HMPA, the resting muscle activity is described as continuous motor unit activity (CMUA) and as repetitive single or grouped discharges. In the 2 families in which rhythmic occurrence of this activity is apparent, it has been compared with neuromyotonia. This is in accordance with the characteristic EMG pattern found by us, consisting of rhythmically repeated duplets and multiplets and which is known as myokymic or neuromyotonic activity (Andermann *et al.*, 1961; Hjorth and Willison, 1973; Albers *et al.*, 1981; Bergmans, 1982).

It appears that while on the one hand this EMG pattern occurs in various clinical syndromes such as myokymia, neuromyotonia and familial CMUA of peripheral origin, on the other hand both in myokymia and neuromyotonia various other EMG patterns have been described. In neuromyotonia the occurrence of bursts is often less rhythmic and in myokymia, in addition to rhythmically occurring duplets and multiplets, short and long bursts that occur irregularly and single action potentials that occur rhythmically or semirhythmically have been described (Denny-Brown and Foley, 1948; Gamstorp and Wohlfart, 1959; Isaacs, 1961; Lütsch *et al.*, 1965; Mertens and Zschocke, 1965; Gardner-Medwin and Walton, 1969; Hughes and Matthews, 1969; Ashizawa *et al.*, 1983).

In our family, we also found rhythmically or semirhythmically occurring single action potentials and irregularly occurring multiplets in addition to the characteristic myokymic discharges. The range of spike frequency is extended beyond 60 Hz, a limit set up by some for myokymic discharges (AAEE Glossary, 1987). However, myokymic discharges

with a high spike frequency have also been described in other syndromes with myokymia, both familial and nonfamilial (Mertens and Zschocke, 1965; Albers *et al.*, 1981; Auger *et al.*, 1984).

The clinical manifestations of the spontaneous muscle activity mentioned in the other families with HMPA, possibly including postnatal contractures, also fit within the range that extends from localized fascicular twitching to generalized stiffness which is encountered in myokymia or neuromyotonia (Isaacs, 1961; Rovetta, 1970; Lütsch *et al.*, 1978; Coërs *et al.*, 1981; McGuire *et al.*, 1984).

Although data are largely incomplete and a variety of aetiologies may exist, many of the characteristics of the CMUA in our family are comparable with those in neuromyotonia and related syndromes. The recruitment of duplets, and triplets on volition, mentioned in 1 other family with HMPA and occasionally observed by us, may be comparable to the repetitive discharges on volition observed in neuromyotonia. Similarly, a short suppression of the CMUA after volition has also been described in neuromyotonia (Stålberg and Trontelj, 1982). The very short suppression of the CMUA following nerve stimulation which we observed, has been reported in familial and nonfamilial examples of CMUA of peripheral origin (Sakai *et al.*, 1983; Auger *et al.*, 1984).

The reduction of myokymic activity by administration of calcium in our patients may be less pronounced than reported in cases of symptomatic myokymia and familial CMUA of peripheral origin, but the increase after hyperventilation seems comparable (Brick *et al.*, 1982; Auger *et al.*, 1984). A decrease of the burst frequency during cooling as we have found has also been reported in familial CMUA of peripheral origin (Auger *et al.*, 1984).

The reaction of the CMUA to ischaemia is not mentioned in the other families with HMPA. In nonfamilial and familial cases of CMUA of peripheral origin, a reduction of amplitude and a decrease in numbers of bursts, burst frequency and number of spikes per burst have been described (Albers *et al.*, 1981; Auger *et al.*, 1984). A rise in the burst frequency during ischaemia as sometimes observed in the present family has not to our knowledge been described before.

The increase in CMUA during treatment with carbonic anhydrase inhibiting drugs, observed in our family, is at variance with a reduction in resting muscle activity by acetazolamide in cases of neuromyotonia (Mertens and Zschocke, 1965). While the resting muscle activity in the nonfamilial and familial varieties of CMUA of peripheral origin is usually reduced by phenytoin, in only 1 of the families with HMPA has a similar effect been observed.

In myokymia, neuromyotonia and hereditary CMUA of peripheral origin, the generation of the resting muscle activity has been localized in distal, proximal or in combined parts of the peripheral nerves (Isaacs, 1961; Mertens and Zschocke, 1965; Hughes and Matthews, 1969; Rovetta, 1970; Irani *et al.*, 1977; Lütsch *et al.*, 1978). In the family described by us, arguments to localize the origin (burst generation) of the distally-recorded CMUA in the peripheral nerves are (1) disappearance after distal and partial disappearance after proximal nerve block, (2) relation between a change in burst frequency during ischaemia and the level of application of the cuff, (3) increase of CMUA following limb ischaemia and (4) alteration of the CMUA induced by a change of temperature applied peripherally. Of other families with HMPA a peripheral neuronal genesis of the resting muscle activity is assumed from histological findings of neuropathy

in one and from the findings of a peripheral nerve block and a curare test in another.

In neuromyotonia the possibility of more than one trigger point along a nerve has been suggested. In the present family a second or third order impulse generation which is different from the primary or burst frequency generation is suggested by (1) the variable presence of small shadow potentials, (2) the independent variation during and after ischaemia of the burst frequency on the one hand and the spike frequency and number of spikes per burst on the other hand and (3) the fact that there is not always a compensatory increase or decrease in burst interval in case of a variable number of spikes per burst. It is conceivable that a second order impulse generation in the nerve is also responsible for the afterpotential at nerve stimulation. This phenomenon has also been described in neuromyotonia and familial CMUA of peripheral origin (Mertens and Zschocke, 1965; Bergmans, 1982; Auger *et al.*, 1984). In our family, the recovery cycle of this after discharge with double stimulation, however, appears to be shorter than has been found in neuromyotonia (Bergmans, 1982). Thus while the various clinical and EMG manifestations of HMPA can be classified within the spectrum of myokymia or neuromyotonia and CMUA of peripheral origin, many similarities exist also with regard to the characteristics of the CMUA, including arguments for a peripheral neuronal generation. In myokymia or neuromyotonia a pathophysiological mechanism has not been defined.

Comparing the data from our family with those of paroxysmal kinesigenic choreoathetosis (PKC), a remarkable similarity can be observed for the kinesigenic stimuli and for the accompanying sensation of stiffness or tense feeling, while some of the characteristics of the attacks such as duration, frequency, age of onset, the tendency to abate in adulthood, are comparable. The favourable reaction to antiepileptic drugs, as in PKC, has not been found by us, but has been seen in 2 of the other families with HMPA. An abnormality in the contingent negative variation, as reported by some in patients with PKC (Franssen *et al.*, 1983; Busard *et al.*, 1984), was absent in our family. With regard to its pathophysiological background, PKC was initially considered to be an epileptic manifestation (Lishman *et al.*, 1962), but later has been classified as a subgroup of paroxysmal choreoathetosis (Kertesz, 1967). A reasonable consensus exists as to involvement of the basal ganglia but, as in HMPA, a consistent structural or metabolic abnormality has not been found (Lance, 1977; Goodenough *et al.*, 1978; Boel and Casaer, 1984).

Familial periodic or intermittent ataxia (FPA) is another syndrome, possibly related to HMPA. Since the first description by Parker (1946), 16 families have been reported with an autosomal dominant inheritance of this syndrome (Farmer and Mustian, 1963; Hill and Sherman, 1968; White, 1969; Griggs *et al.*, 1978; Donat and Auger, 1979; Wolf, 1980; Margolin *et al.*, 1981; Aimard *et al.*, 1983; Zazorin *et al.*, 1983; Bouchard *et al.*, 1984; Trillet *et al.*, 1985; Friedman and Hollmann, 1986; Gancher and Nutt, 1986; Nespeca *et al.*, 1987). Major and minor differences between these families point to heterogeneity in this group. Comparing the data of our family with those of FPA, resemblance is found for the intermittent ataxia and the prevention of these attacks by acetazolamide. Different are the long duration of the attacks in FPA and the presence of vertigo, nausea and sometimes headache during the attacks. Also notably different is the presence of nystagmus both during and between the attacks. In FPA attacks are often provoked by exercise and by alcohol. A kinesigenic provocation is mentioned

only twice and a sensory aura is unusual. The pathophysiology of FPA is not clear. A disorder of pyruvate metabolism, known to cause intermittent ataxia (Lonsdale *et al.*, 1969; Blass *et al.*, 1970; Sander *et al.*, 1980), has been reported in 1 family with X-linked intermittent ataxia (Livingstone *et al.*, 1984) and in 1 family with autosomal dominantly inherited FPA (Nespeca *et al.*, 1987). Atrophy of the cerebellum or of the cerebellar vermis has been demonstrated in these 2 families and in 1 other family with FPA (Vighetto *et al.*, 1988). In HMPA, normal venous pyruvate and lactate levels in 1 family add to the improbability of a disorder of pyruvate metabolism.

Acetazolamide has not only been used to prevent attacks in FPA, but also in nonfamilial paroxysmal ataxia (Voiculescu *et al.*, 1975; Verlooy and Velis, 1985) and in several paroxysmal dyskinesias (Mayeux and Fahn, 1982; Fahn, 1983; Fahn and Bressman, 1983). In FPA it has been suggested that the influence of acetazolamide on pyruvate metabolism may play a role (Evans *et al.*, 1978; Zazorin *et al.*, 1983; Livingstone *et al.*, 1984) and also that its effect is caused by its carbonic anhydrase inhibiting action (Wolf, 1980). The comparable effectiveness of acetazolamide and sulthiame in our family with HMPA supports the idea that inhibition of carbonic anhydrase plays a role. In the brain carbonic anhydrase is present in the choroid plexus and in glia (Giacobini, 1962; Maren, 1967). In lower doses, acetazolamide has an anticonvulsant action probably caused by a local accumulation of CO₂ in neurons and a hyperpolarization of the glia cell membrane (Woodbury *et al.*, 1982; White *et al.*, 1986). Conceivably, its effect in the prevention of attacks of ataxia is related to this effect on neuronal excitability which thus may well be aspecific. The occurrence of paraesthesiae and increase in myokymic activity, encountered as side effects in our patients, cannot be understood from local carbonic anhydrase inhibition, as this enzyme has not been demonstrated to be present in peripheral nerves. The alterations in pH and potassium homeostasis, the shift in serum anion concentrations and retention of CO₂ may play a role here.

In our view, the data from the comparison with PKC and FPA do not contradict the idea, supported by comparison with neuromyotonia, that in HMPA alterations of neuronal membrane properties exist and that it can be regarded as a disorder of membrane function.

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APPENDIX 1

Data concerning attacks based on medical histories*

	Generation III										Generation IV										Generation V									
	24	25	26	31	32	33	34	35	37	39	9	12	13	15	17	21	22	24	1	3	5	11	13	15						
Year of birth	20	24	30	19	21	22	24	27	32	35	47	46	48	46	57	54	58	58	74	66	73	79	75	76						
Age of onset (yrs)	7	7	7	15	8	8	8	4	8	12	6	6	3	4	7	8	2	2	5	4	6	3	8	5						
Frequency /yr		3		3				4	0				0	2	0	0		0												
range /mo	1	1		1	1		1			4	1						1		4	1	2	1	1	1						
/wk			1				3	2		3	2	2	1		3	1			2		2	1								
/d	1		3					1				1	1				5	15	2		4			2	15					
Duration s	5	15									5	5							30		10	10								
range min			5	2	5	10	5	1	3	3	1	5	3	2	2	1	3	3	2	3	3	8	4							
max			10	3	10	15	15	5	4	10	6		4	3	8	10	5	30		5										
h	6	6																												
Sensory aura	1	1	-	1	0	5	2	-	2	2	0	-	-	2	-	-	10	0	-	-	0	-	10	-						
range s	3	2		3		30			10	10			5																	
Symptoms																														
Vertigo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	-	-	0	0	-	-						
Blurred vision	+	+	+	+	+	+	+	+	+	+	±	-	-	-	+	+	+	0	-	-	0	0	-	-						
Diplopia	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	0	-	-	0	0	-	-						
Searing of eyes	-	-	+	+	-	+	+	+	-	+	-	+	+	+	-	+	+	0	-	-	0	0	-	-						
Stiffness																														
Face/tongue	-	+	+	+	-	±	+	+	+	+	-	+	-	0	-	±	±	0	+	+	0	0	-	-						
Extremities	-	-	+	+	+	+	+	+	+	+	-	±	-	0	+	+	+	0	+	+	0	0	-	-						
Trembling																														
Face	+	+	+	+	+	+	+	0	+	+	+	+	-	0	+	+	-	0	-	-	0	0	-	-						
Head	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	0	0	+	+							
Extremities	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	0	0	+	+							
Autonomic signs																														
Sweating	-	+	-	+	-	+	+	0	+	-	-	+	-	0	+	-	-	0	-	-	0	0	-	-						
Nausea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	-	-	0	0	-	-						
Disturbed stance	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+							
Disturbed gait	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	+	+							
Disturbed hand/arm	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	0	0	+	+							
Disturbed speech	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	0	0	+	+						
Provocation																														
Spontaneous occurrence	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Sudden movements	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	0	+	+							

APPENDIX 3

Additional investigations and treatment

	Generation III										Generation IV								Generation V					
	24	25	26	31	32	33	34	35	37	39	9	12	13	15	17	21	22	24	1	3	5	11	13	15
Additional investigations																								
Abnormal blood chemistry	—	—	0	0	0	—	—	0	—	—	0	—	—	—	—	0	—	—	0	0	0	—	0	0
Abnormal blood gases	0	—	0	0	0	—	—	0	0	—	0	0	0	0	—	0	0	0	—	0	0	0	0	—
Abnormal EEG	—	0	+	0	0	0	0	0	+	0	0	0	+	0	0	0	—	+	—	—	0	0	0	—
epilepsy			+										★					+						
Abnormal CNV	0	0	0	0	0	0	0	0	0	0	—	0	0	—	0	0	0	0	—	0	0	—		
Abnormal CT	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal MRI	0	0	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Myokyma on EMG	+	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+	+	0	+	+	0	+	+	+
Drug treatment*																								
Phenobarb	0	0	?	0	0	0	0	0	0	0	0	?	0	0	0	0	—	0	0	0	0	0	0	0
Phenytoin	0	★	★	0	0	0	0	0	0	★	±	0	0	0	0	—	?	—	0	0	0	0	0	0
Carbamazepine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0	0	—	0	0	0	0	0
Clozapem	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?
Cocaine	★	0	0	0	0	0	0	0	0	0	★	0	0	0	0	0	0	0	0	0	0	0	0	0
Clozapemine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	★	0	0	0	0	0	0
Carbonic anhydrase inhibitors																								
Acetazolamide	0	?	?	0	0	+	+	0	0	+	?	0	0	+	+	+	0	0	★	+	0	+	0	0
Diclofenamide	0	?	0	0	0	0	0	0	0	0	?	0	0	0	0	0	0	0	?	0	0	0	0	0
Soldazone	0	0	?	0	0	+	+	0	0	+	+	0	0	?	+	0	+	0	+	?	0	0	+	+

* + = marked improvement, ★ = uncertain improvement, ? = duration too short, — = unaltered attack frequency; 0 = unknown

APPENDIX 4

Hereditary paroxysmal ataxia and myokymia

	Van Dyke et al (1975)	Hansen et al (1977)	Ganchev and Nutt (1986)	Brunt and van Weerden (1990)
Inheritance	AD	AD	AD	AD
Number reported	3	3	3	22
estimated	7	3	7	22
affected	11	4	15	28
Ataxia				
Age of onset (yrs)	2–12	4–8	6–15	2–15
Ataxiometer	?	?	>20	20–50
Frequency/d	0–10	0–1	0–2	0–15
Duration	±3 min	10–15 min	±2 min	10 s–10 min some up to 6 h
Subjective sensations	Sensory warning + vertigo, dizziness, blurred vision, diplopia	Sensory warning + weakness legs, eyes drawn backward	Sensory warning + weightlessness, sensation of falling	Sensory warning ± lump, stiffness, heavy feeling, trembling, blurred vision ±
Movements/coordination	Generalized ataxia, jerking, nodding of head and arms	Generalized ataxia, shaking, staggering	Generalized ataxia, tremor +	Generalized ataxia, postural tremor head/arms ±
Stiffening	Generalized myokymia, carpal spasm	Stiffening and cramp in body, arms and hands	Twitching in limb muscles, puckering mouth	Sometimes stiffening in the hands
Provocation	Kinesogenic + caloric stim +	Kinesogenic + caloric stim —	Kinesogenic + caloric stim ?	Kinesogenic + caloric stim ?
Additional influences	Hunger, fatigue, excitement, anxiety	Perimenstrual, illness	Exercise, stress, trauma, fatigue, excitement	Stress, excitement, illness

Prevention by avoiding strain	Yes	Unknown	Unknown	Yes
Interval examination	—	—	—	—
Nystagmus	?	?	?	± few, >50 yrs
Ataxia	> 12 yrs	Adult: resting tremor in body and hands, Children: slight finger tremor	Adolescence: face, distal limbs, moving fingers	>20 yrs in most heads, face, in some children: pendular finger movements
Myokymia	carpal spasm, calf hypertrophy	Neonatal foot, hands	Foot abnormality	None
Contractures	None	CMUA, repetitive normal/polyphasic and grouped discharges	shortened tendon	All examinations irregular/regular repeated singlets/multiplets
EMG	CMUA		Neuromyotonia: repetitive grouped discharges, rhythmic singlets	
Treatment				
Phenytoin	ataxia \, myokymia —	ataxia \, myokymia —	Ataxia —, myokymia \	Ataxia —, myokymia ?
Acetazolamide	ataxia ?, myokymia ?	ataxia ?, myokymia ?	Ataxia —, myokymia ?	Ataxia \, myokymia /
Investigations				
Laboratory	normal	CK ± elevated	Normal	Normal
Muscle biopsy	type I predominance	some small fibres	Neurogenic change	Normal (H-E stain)
Nerve biopsy	axonal loss	n d	Normal	Normal
	peripheral neuropathy			
Brain macroscopy	n d	n d	n d	Normal

— = absent, AD = autosomal dominant, CMUA = continuous motor unit activity, n d = not done, — = no change, \ = decrease, / = increase

THE COMPORTMENTAL LEARNING DISABILITIES OF EARLY FRONTAL LOBE DAMAGE

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SUMMARY

Two adult patients are described who suffered bilateral prefrontal damage early in life and who subsequently came to psychiatric attention because of severely aberrant behaviour. A battery of developmental psychology paradigms (not previously used to assess neurologically impaired individuals) showed that social and moral development of these 2 patients was arrested at an immature stage. In comparison with other types of brain damage which disrupt cognitive development, frontal damage acquired early in life appears to provide the neurological substrate for a special type of learning disability in the realms of insight, foresight, social judgement, empathy, and complex reasoning.

INTRODUCTION

Most of the available literature on the behavioural affiliations of the human frontal lobe is based on the clinical examination of patients with lesions acquired during adulthood (Ackerly, 1935; Brickner, 1936; Hebb, 1945; Benton, 1968; Milner, 1982; Eslinger and Damasio, 1985; Lhermitte, 1986; Lhermitte *et al.*, 1986). Comparatively little information is available about the behavioural outcome of lesions acquired early in life or in the course of embryogenesis. Such information could help to identify the behaviours that depend on the frontal lobes for their acquisition and development.

This report describes 2 individuals who sustained severe frontal lobe damage early in life and subsequently displayed major behavioural abnormalities as adults. These observations suggest that the frontal lobe plays an essential role in the maturation of complex comportmental skills, formal operational thought, social conduct and moral judgement.

CASE REPORTS

Case 1

G.K. is a 31-yr-old right-handed man who has been given multiple diagnoses, including antisocial or borderline personality, atypical psychosis, and paranoid schizophrenia. Because of increased head circumference over the first 7 days of life, bilateral ventricular punctures were performed which yielded 10 ml of subdural haematoma fluid. Air was injected after aspiration and an irregular collection in the left frontal lobe was demonstrated. He was discharged 7 wks after birth when his head circumference had stabilized and he was thriving.

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Detailed history from multiple sources revealed that he was always considered immature but that serious behavioural difficulties were first identified by the age of 8 yrs. He did not respond to parental discipline, always sought gratification of his immediate needs, never developed adequate friendships, and blamed his difficulties on others. Though gregarious, he was irresponsible, tended to wander, and consistently fell under the influence of other deviant children. Under firm guidance and after two school transfers, he graduated from high school. He joined the Marine Corps but was dishonourably discharged 6 wks later. Over the next 10 yrs, he was hospitalized 27 times in psychiatric institutions and imprisoned 8 times on charges of assault, forgery (using his father's cheque book), grand larceny, drug involvement and lewd behaviour. Inappropriate behaviours were numerous. While walking by a gas station he saw an unattended taxi with keys in the ignition. He jumped in and drove off, ripping the hose from the gas pump, only to be captured several blocks away. When restricted for inappropriate behaviour by a ward attendant, he escaped from the locked psychiatric unit, scratched the attendant's car with broken glass, signed his own name, and re-entered the ward. When confronted, he denied his involvement. The only 2 people he claimed as friends were involved with him in abusing marijuana, alcohol, LSD, and phencyclidine. He was charged with arson of two public buildings. He is an active bisexual, often trades cigarettes for oral sex, and masturbates in public. He was a suspect in the rape of 2 female ward patients. Neither individual psychotherapy nor trials on multiple psychoactive agents were effective.

The patient has 5 younger brothers. One suffers from mild mental retardation of unknown aetiology. Four siblings are college graduates, 1 is a lawyer. His father successfully operates a landscape business. His mother was trained as a nurse and suffers from depression and alcoholism. There is no other significant family psychiatric history. The family environment was not particularly chaotic or stressful.

Neurological examination revealed an overly familiar, impulsive, but cooperative man. He showed little insight or empathy and felt victimized by others. Other than a minimal left central facial paresis, the examination was unremarkable, without grasp, suck or root reflexes. Formal neuropsychological testing revealed a WAIS-Revised verbal IQ of 102, Performance IQ of 90, and Full-Scale IQ of 96 (Wechsler, 1981). No primary memory, language or visuospatial difficulties were demonstrated. Deficits were confined to attentional, organizational, and mental flexibility skills. For example, severe deficits were seen on Part B of the Trail Making Test (Reitan, 1958), Stroop Interference (Stroop, 1935), Wisconsin Card Sorting (Berg, 1948), Luria hand-motor sequences (Luria, 1973), auditory go-no-go (Luria, 1973), and the visual-verbal test (Feldman and Drasgow, 1959). Word list generation (Benton and de Hamsher, 1976), and traditional office tests of abstraction and proverb interpretation were normal (Table 1).

General medical examination, laboratory tests, and routine EEG were normal. Axial MRI images using T1 and T2-weighted sequences revealed bilateral lesions extending from cortex to the caudate nuclei, more on the left than the right. There was mild ex vacuo enlargement of the right lateral ventricle (fig. 1).

TABLE 1 NEUROPSYCHOLOGICAL PROFILE OF CASE 1

<i>Test</i>	<i>Score</i>	
WAIS-R		
Verbal IQ	102	Average
Performance IQ	90	Average
Full Scale IQ	96	Average
Digit Span	7 forward/4 backward	Mild inattention
Word Generation (F/A/S)	17/7/11	57th percentile
Stroop Interference	143 s/6 errors	< 1st percentile
Trails B		< 1st percentile
Wechsler Memory Scale	86*	18th percentile
Boston Naming Test	54/60	31st percentile
Hooper Visual Organization Test	14/15	Normal
Visual-Verbal Test	0/5	Abnormal

* Although the Wechsler Memory Scale suggests low average memory, no memory difficulties were apparent in his daily living activities.

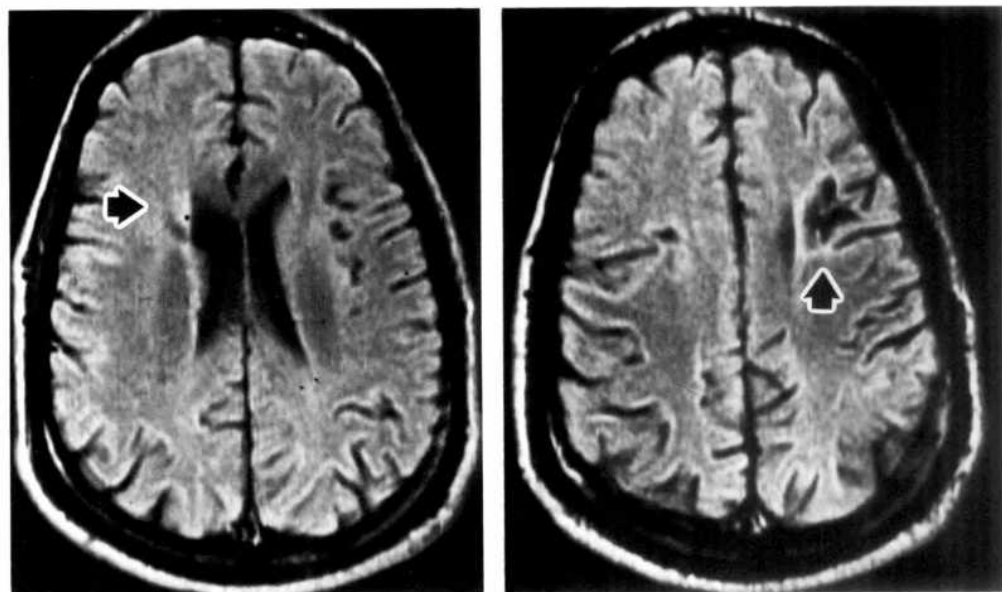


FIG. 1. *Case 1.* Axial MRI scan showing bilateral frontal lobe lesions. The left side of the head is on the right of the scan. Left involvement is greater than right. The lesions extend from cortex to the caudate nuclei. Mild ex vacuo enlargement of the right lateral ventricle can be seen.

Case 2

M.H. is a 26-yr-old ambidextrous woman who was referred by the Massachusetts Department of Social Service for inappropriate behaviour and negligent care of her 2½-month-old infant. She was developing appropriately until 4 yrs of age, when she was struck by an automobile. She was unconscious for 48 h and suffered bilateral skull fractures and a right frontal haematoma.

Over the next year she began to exhibit temper outbursts when frustrated. She became verbally and physically assaultive in an abrupt, unpredictable, and short-lived manner. She hit her brother, threw her father over a table, and cut her sister with glass. Family members lived in constant terror and once called the police when she threatened them at knife point. She repeated the first and second grades and was given special tutorials in English, social studies, and reading. She graduated from high school at age 20 yrs. Since her early teens, she was known for her sexual promiscuity and bravado. She intermittently engaged in heavy alcohol and marijuana use. She had no sustained friendships.

After high school graduation, she held several temporary menial jobs where infrequent outbursts against coworkers or customers occurred. Although free of major depressive symptoms, she impulsively attempted suicide twice, once with an overdose of hypnotics, and another time by jumping out of a second floor window.

At age 17 yrs, she was raped while wandering through a local cemetery, but returned to the scene and was raped again by the same man. Her first pregnancy was terminated by an elective abortion, another ended in miscarriage, and her third accidental pregnancy yielded a daughter despite her parents' and boyfriend's pleas for an abortion. She under-dressed the baby in inclement weather, fed her erratically and left her unsupervised for lengthy periods of time. There were suspicions of physical assault. At 20 days of age, the patient's daughter was placed in foster care. This intervention infuriated the patient who saw nothing wrong with her child care. She attacked the social worker, and threatened to kill members of the social service agency. At her last follow-up visit in our unit, she was pregnant again but was uncertain who the father might be. Individual psychotherapy did not significantly alter her behaviour nor did a prolonged trial of anticonvulsant agents.

The patient is the fourth of 6 children. None of her 5 siblings has similar behavioural problems. Her father is an optician and her mother is employed as a purchasing agent. Besides the father's occasional alcohol abuse, there is no history of psychiatric disease in the family.

Neurological examination revealed a somewhat diffident, but cooperative woman with limited insight. Other than skull deformities over the right orbit and temporal region, and a slightly increased left knee jerk, examination was normal.

WAIS-Revised testing estimated a Verbal IQ of 78, Performance IQ of 83, and Full Scale IQ of 78 (Wechsler, 1981). No deficits in memory or visuospatial abilities were noted. WRAT performance revealed deficiencies in reading (23rd percentile), spelling (32nd percentile) and mathematics (4th percentile) (Jastak and Jastak, 1965). Attention was slightly impaired with a digit span of 6 forwards and 6 backwards (Wechsler, 1981) and a Corsi block span of 5 forwards and 5 backwards (Milner, 1971). She identified 40 of 60 pictures on the Boston Naming Test plus 6 given additional naming cues (Kaplan *et al.*, 1978). Moderate impairment was seen on tests of mental flexibility, sustained effort and abstract reasoning, such as the Trail Making Test, Part B (Reitan, 1958), Stroop interference (Stroop, 1935), word list generation (Benton and de Hamsher, 1976), visuoverbal (Feldman and Drasgow, 1959), and proverb interpretation tests (Table 2).

A 1980 routine awake EEG while the patient was on phenytoin was normal. An axial MRI scan revealed abnormal T1 and T2 signal intensities in both prefrontal regions with dilatation of frontal horns, greater on the left (fig. 2).

TESTS OF PSYCHOLOGICAL DEVELOPMENT

Logical thought, role-taking ability, social and moral reasoning undergo predictable stages of development which can be assessed quantitatively with the help of paradigms that have been validated extensively in many normative populations. We used these paradigms to test our 2 patients.

Piaget (1968) has shown that children go through stages of cognitive development which are characterized by successively more complex modes of information processing (i.e., thinking). According to Piaget's nomenclature, children undergo a sequence of cognitive development from sensorimotor (0-2 yrs) to preoperational (2-5 yrs), concrete operational (6-10 yrs) and then formal operational thinking. Formal operational thinking (age 11 yrs to adulthood) is based on hypothetical, deductive and propositional thought which allows the individual to predict the divergent outcomes that could result from a given set of actions. Research has indicated that the vast majority of middle class Americans exhibit major components of formal operational thought by their early twenties (Kohlberg and Gilligan, 1971).

TABLE 2 NEUROPSYCHOLOGICAL PROFILE OF CASE 2

Test	Score	
WAIS		
Verbal IQ	78	Borderline
Performance IQ	83	Low average
Full Scale IQ	78	Borderline
Digit Span	6 forward/3 backward	Mild inattention
Word Generation (F/A/S)	13/9/5	27th percentile
Stroop Interference	74 s/7 errors	51st percentile in time, no errors is norm
Trails B	99 s/0 errors	< 2nd percentile
3 words/3 shapes* (10 and 30 min delay)	6/6	Normal
Boston Naming Test	40/60 (46/60 with cues)	18th percentile
Hooper Visual Organization Test	26/30	Normal
Visual-Verbal Test	4/5	Normal

* This test is based on 3 sample designs and 3 words with low imagery value. Immediate incidental recall and recall after 10 and 30 min were intact (Weintraub and Mesulam, 1985)

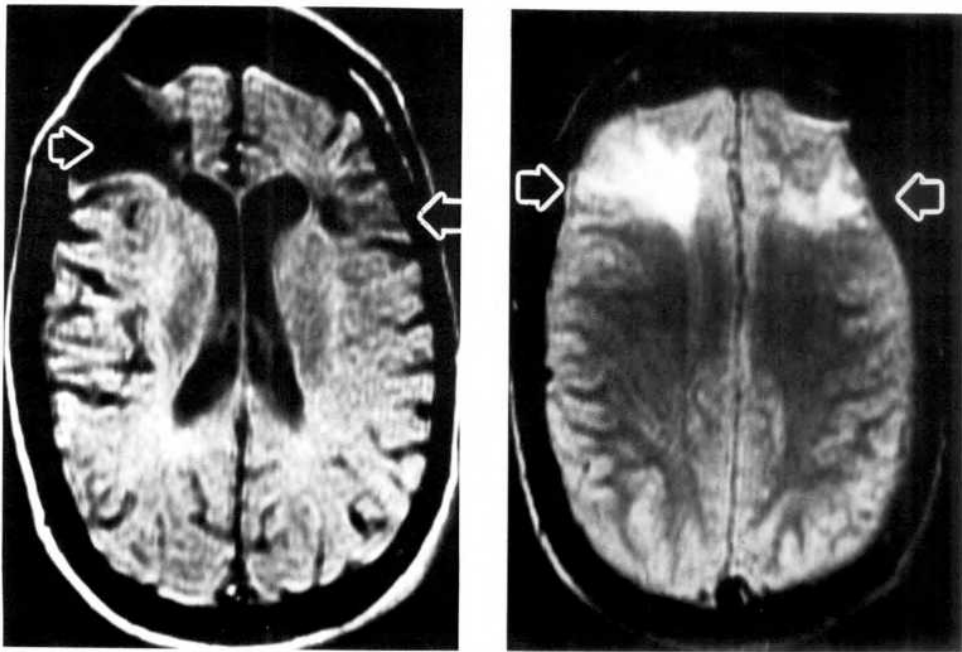


FIG. 2. Case 2. Axial MRI scans using T1 and T2 pulse sequences showing extensive damage confined to the frontal lobes. The left side of the head is on the right of the scan. Frontal horn dilatation is present, greater on the left.

Both our patients were able to perform a concrete operational task based on the recognition that the quantity of water remains unaltered when it is poured from a tall, narrow flask to a short but wider container. Neither patient, however, demonstrated formal operational thinking on the cognitive task described below.

Kuhn developed a problem based on presenting the subject with 4 plants, of which 2 look healthy and 2 unhealthy (Kuhn and Brannock, 1977). Each plant has been cared for in a different way with a combination of 1 of 2 kinds of plant food and 1 or 2 different amounts of water, with or without leaf lotion (fig. 3). The problem is constructed so that only one variable (plant food) determines the plant's health. In Kuhn's study of middle class students, only 15% of sixth graders failed to demonstrate any level of formal operational thought. Both our patients focused their attention on the problem but scored at the concrete operational level. They were unable to isolate the critical variable and failed to demonstrate formal operational thinking.

Selman (1971) has shown that a child is initially unable to differentiate his own perspective from that of another. Subsequent development allows the child to assume other perspectives and roles. The development of interpersonal empathy is presumably also dependent on the emergence of this capacity.

To investigate our patients' role-taking ability, a task developed by Flavell (1968) was given. It is performed by presenting the subject with a simple map and telling him that it is identical to one held by someone else lost in the countryside. The task requires the subject to take into account the location of the lost person, to suppress an egocentric perspective and, instead, to imagine how the lost person might interpret the message and respond to the instructions (fig. 4). Flavell demonstrated that while 75% of third graders found no more than 1 error, by the seventh grade 45% had found 2 errors and 40% 3 or all of the 4 errors. Both our patients found the task engaging and carefully read the directions. Case 1 found only 2 errors. Case 2 was unable to recognize any errors saying 'The directions were fine'.

Kohlberg has described 6 stages of moral development based on a longitudinal study over the past 30 yrs of 50 American boys (Kohlberg and Gilligan, 1971; Kohlberg, 1976) (Table 3). Studies suggest that by adolescence nearly 80% of middle class American boys have developed beyond preconventional moral reasoning (Kohlberg and Gilligan, 1971).



FIG. 3. Kuhn's plant problem. Two healthy and 2 dying plants are shown with different combinations of water volume, plant food (black and white), with or without leaf lotion. The subject's task is to isolate the one crucial variable (plant food) that determines the plant's health while excluding the inoperative variables (water and leaf lotion). Reproduced from Kuhn and Brannock (1977) with permission.

The 'Heinz dilemma', one of the paradigms used to assess moral development, asks the subject whether or not someone should steal a drug to save his dying wife. Case 1 responded at Kohlberg's early conventional level (stage 3), stating that Heinz should steal the drug 'because his wife is dying and human life is more important than money'. When asked why that should be, he responded 'because it is sacred. God put everyone on earth to do the best that he or she can and to help everyone out'. His reasoning about real life dilemmas revealed a more primitive preconventional orientation. After having impregnated a vulnerable and disturbed woman, his main concern was that 'Her father looked like Mean Joe Green. I wondered whether I would be killed now or later'. Case 2 responded to the Heinz dilemma at stage 1 of the preconventional level, and concentrated on her concerns about punishment. Heinz should not steal the drug because 'if you do it you're going to end up in jail. Then you'll fry in the electric chair'. At this primitive level, human interactions are viewed in physical, not psychological terms. People are seen as avenues or obstacles to gratification.

DISCUSSION

We have described 2 patients, aged 28 and 24 yrs at the time of our examination, who sustained brain injury at birth and 4 yrs of age. While we cannot be certain about the precise extent of the lesions, the neurodiagnostic, neurological and neuropsychological examinations indicated that the principal (if not exclusive) site of involvement was located bilaterally in the frontal lobes. Both patients displayed impulsive behaviour triggered by the immediate stimulus, performed with childish abandon and shallow foresight. Neither was able to learn from negative experience or punishment. Each patient remained

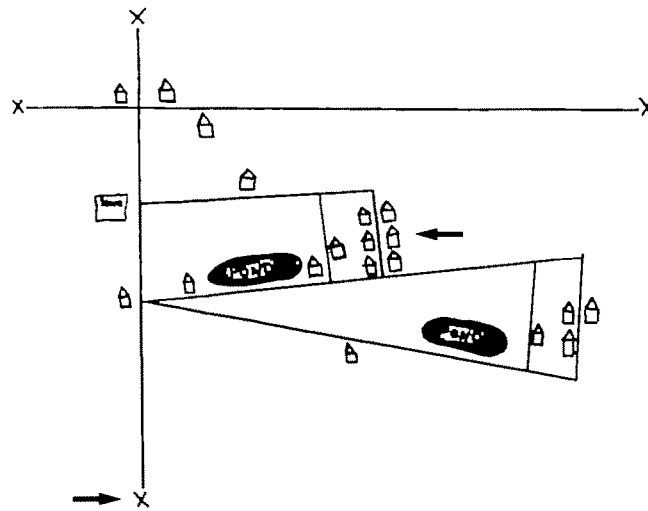


FIG. 4 Flavell's role-taking map test. The subject is instructed as follows. 'Now suppose there were a man in his car out in the country some place who got lost—he didn't know where he was or how to get to the house he wanted to go to. Now suppose he had this map (points) and I had *exactly* the *same* map here (points). Now he calls me up on the telephone and from what he says I can figure out where he is now. He is here (points to bottom X on the map, and I can also tell him how to get to where he wants to go—there (points to second house on the right on the street which contains a cluster of six houses). I'm going to read out loud what I might tell him over the phone, and you may look along with me as I read. When I get through I want you to tell me what's *wrong* with the way I gave him the directions, why he'd have trouble getting there from what I say. Okay, now I'm going to talk to him on the phone.' The message is slowly read. 'If you look on your map you'll find an X. That's where you are right now. You go down the road until you see a house on your left. Turn right there and keep going until you pass a pond on your left. Then you make a left turn and the house you want is the second one on the street.' The subject is then asked to identify the ambiguities (total of 4) which might prevent the lost person from reaching the destination. The map is shown to the subject minus the designations of the lost person's present location (—) and destination (—). Reproduced from Flavell (1986) with permission.

socially isolated without enduring friends, had little sense of remorse, empathy or fairness towards others but, instead, felt victimized. Both responded to firm parental and school guidance, but never acquired self-governance over their behaviour. Neither was raised in a particularly chaotic environment which could account for their life-long behavioural problems. Neither benefited from prolonged psychotherapy or medications. In comparison with the severe deficits of comportment, judgement and insight, neither patient displayed limiting deficits of language, memory or visuospatial skills in daily activities. The salient behavioural features in these patients are qualitatively similar to but appear quantitatively more intense than the behavioural deficits that emerge as a consequence of bilateral frontal lobe lesions acquired in adulthood.

Ackerly and Benton (1948) presented a 35-yr-old man who sustained bilateral frontal lobe damage around 3 yrs of age. The patient had 'normal' intelligence (Stanford-Binet IQ 92) but displayed behavioural abnormalities very similar to those in our patients. These included immaturity, inability to learn from experience, diminished insight, immersion in the present, lack of drive and curiosity, and irritability when crossed or restricted. When retested 15 yrs later, his behaviour remained unchanged (Ackerly, 1964). Russell (1959) briefly mentioned a boy who at 5 months of age sustained frontal

TABLE 3 STAGES OF MORAL DEVELOPMENT ACCORDING TO KOHLBERG (1976)*

<i>Stage</i>	<i>What is considered to be right</i>
Stage 1. Obedience and punishment orientation	To avoid breaking rules backed by punishment, obedience for its own sake, avoiding physical damage to persons and property
Stage 2. Instrumental purpose and exchange	Following rules only when it is to someone's immediate personal interest, acting to meet one's own interests and letting others do the same; right is an equal exchange, a good deal
Stage 3. Interpersonal accord and conformity	Living up to what is expected by people close to you or what people generally expect of people in your role, being good is important
Stage 4. Social accord and system maintenance	Fulfilling the actual duties to which you have agreed; laws are always to be upheld except in extreme cases where they conflict with other fixed social duties; right is also contributing to society, the group, or institution
Stage 5. Social contract, utility, individual rights	Being aware that people hold a variety of values and opinions, that most values and rules are relative to your group but should usually be upheld because they are the social contract; some nonrelative values and rights like life and liberty, however, must be upheld in any society regardless of the majority opinion
Stage 6. Universal ethical principles	Following self-chosen ethical principles, particular laws or social agreements are usually valid because they rest on such principles; when laws violate these principles, one acts in accordance with the principle; principles are universal principles of justice; the equality of human rights and respect for the dignity of human beings as individual persons: the reason for doing right is the belief, as a rational person, in the validity of universal moral principles and a sense of personal commitment to them

* Stages 1 and 2 characterize the preconventional level. Stages 3 and 4 represent the conventional level. Stages 5 and 6 occur at the postconventional level. Reproduced from Snarey (1985) with permission.

lobe damage from a bomb fragment. Severe behavioural problems were subsequently noted, including physical attacks on smaller children and the school cat, stealing, eating refuse, and deliberately emptying tea on his bed. His brothers and sisters were reportedly normal. A preliminary report describes a third case of early frontal injury leading to comportmental abnormalities during adulthood (Eslinger *et al.*, 1989).

Recent evidence suggests that a specific learning disability such as dyslexia may be associated with developmental or early-acquired structural abnormalities located predominantly in the left hemisphere (Galaburda, 1988). Analogous involvement of the right hemisphere may lead to shyness, chronic emotional difficulties, poor paralinguistic abilities, and impaired visuospatial skills (Weintraub and Mesulam, 1983). Our 2 patients, as well as the additional case reports mentioned above, suggest that a third type of learning disability, associated with bilateral prefrontal lesions, may lead to major deficits in the maturation of judgement, insight, foresight, abstract reasoning, perspective taking, empathy and moral development.

Anatomical and physiological observations show that the prefrontal cortex provides a template for the convergence of limbic inputs with extensively processed associative

information (Mesulam, 1986). This part of the brain is likely to provide one of the most important components of a neural network underlying the integration of thought with emotion (Mesulam, 1985, 1988). The behavioural deficits displayed by our 2 patients are in keeping with the disruption of such a network.

The determinants of functional recovery after brain damage are not fully understood. In a large sample of patients who suffered profound damage to the left hemisphere before the age of 5 yrs most language functions appeared to have developed normally when the subjects were subsequently tested (Lenneberg, 1967). Only subtle deficits emerged when such patients were challenged with more difficult language tasks (Dennis and Whitaker, 1976). Equivalent lesions acquired during adulthood would be expected to yield much more severe and permanent aphasias. A different temporal relationship appears to characterize the impact of frontal lobe damage. Our 2 patients suggest that early bilateral frontal lesions may leave permanent uncompensated deficits that persist into adulthood. It even appears as if bifrontal lesions yield behaviours that are more chaotic and aberrant when the damage is acquired early in life rather than during adulthood.

Our patients' lack of premeditation, the remarkable clumsiness in committing crime, and the lack of predisposing factors in the social background distinguish them from others who are designated as sociopaths. The extent to which frontal lobe lesions underlie deviant and criminal behaviour in the general population is difficult to surmise. Several investigations of incarcerated juvenile delinquents have reported a profile of neuropsychological deficit that resembles the pattern displayed by our 2 patients (Moffitt and Silva, 1988). A recent study of juveniles condemned to death revealed that the majority had a history of head trauma, EEG abnormality and abnormal performance in tests of reasoning and mental flexibility (Lewis *et al.*, 1988). Conceivably, a subset of these individuals could have underlying bifrontal dysfunction acquired early in life or even during the stage of prenatal development. In some of these cases, the dysfunction could be at a neurochemical or physiological level not detectable by conventional neurodiagnostic methods.

The 2 patients described in our report show that bifrontal dysfunction acquired early in life may lead to a specific subtype of learning disability by selectively interfering with the acquisition (or development) of many complex faculties such as insight, foresight, social judgement, empathy and abstract reasoning. Diagnosis may be particularly challenging. The predominantly behavioural presentation in the absence of focal elementary neurological signs may lead to the erroneous impression that the underlying factors are primarily psychiatric or environmental.

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CEREBRAL BLOOD FLOW IN PROGRESSIVE APHASIA WITHOUT DEMENTIA

CASE REPORT, USING $^{133}\text{XENON}$ INHALATION, TECHNETIUM 99m
HEXAMETHYLPROPYLENEAMINE OXIME AND SINGLE PHOTON
EMISSION COMPUTERIZED TOMOGRAPHY

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SUMMARY

We report a case of progressive aphasia without clinical signs of intellectual or behavioural impairment, satisfying Mesulam's clinical criteria of primary progressive aphasia, as 4 yrs of extensive psychometric testing and radiological imaging, comprising CT and MRI, failed to detect evidence of relevant involvement outside the left perisylvian regions. Cranial CT was normal but MRI showed multiple bilateral lesions in the deep white matter. Cerebral blood flow (CBF) studies by single photon emission computerized tomography, however, showed an initial frontotemporal focus of hypoperfusion that progressively extended to include most of the ipsilateral hemisphere and the contralateral frontal lobe. This suggests that CBF imaging may yet be the most sensitive technique in revealing subclinical injury in the degenerative brain diseases of focal onset.

INTRODUCTION

Mesulam (1982) described a syndrome of slowly progressive aphasia, evolving over 5 to 11 yrs in 6 patients. It was characterized by insidious onset, and developed into severe anomic aphasia without intellectual or behavioural impairment. Although no pathological data were available, he suggested that it was due to a focal degenerative lesion in the left perisylvian region, and considered it a disease apart from the primary degenerative diseases, later naming it primary progressive aphasia (Mesulam, 1987). The aetiology and very existence of this new syndrome were quickly disputed, some authors considering progressive aphasia to be the initial clinical manifestation of more diffuse cerebral pathology of vascular (Benson *et al.*, 1982) or degenerative origin such as Pick's (Wechsler *et al.*, 1982) or Alzheimer's disease (Foster and Chase, 1983; Gordon and Selnes, 1984). Few modern postmortem examinations of primary progressive aphasia (PPA) have been reported (Wechsler *et al.*, 1982; Holland *et al.*, 1985; Kirschner *et al.*, 1987); their conflicting results suggest that this syndrome may cover a wide spectrum of aetiologies.

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We report a case of progressive language impairment evolving over 4 yrs into a nonfluent aphasia with components of severe anarthria, without intellectual or behavioural disturbances, the evolution of which was followed by serial blood flow studies employing single photon emission computerized tomography (SPECT). Whereas the clinical deficit remained functionally limited to a left perisylvian locus, the CBF studies demonstrated a frontotemporal focus of hypoperfusion, that was followed by a flow decrease in larger parts of the dominant hemisphere, later extending to the nondominant frontal lobe.

CASE REPORT

A 67-yr-old right-handed Caucasian woman was admitted in May 1985 because of progressive aphasia for 1 yr with a rapid although not an acute onset which impaired speech fluency and articulation. It did not affect reading or calculation, and the patient remained professionally active as a shop cashier. Family history, personal history and general physical examination were unremarkable but for a 5 yr history of moderate systemic hypertension, treated by diuretics. Neurological examination was normal except for nonfluent aphasia.

Neuropsychological examination on admission confirmed the existence of deficiencies in spontaneous speech, with impaired fluency, prosody and articulation. Specific aphasia testing revealed impaired sentence repetition, and discrete naming difficulties with slow responses and distorted articulation. Reading was characterized by word omissions and additions. Spelling was slightly affected, and writing somewhat dysorthographic and agrammatic with word inversions. A printed text was transcribed to handwriting without

TABLE 1 OBSERVED : SCORE POINTS AND DIFFERENCE SCORES* IN THE STANDARDIZED NEUROPSYCHOLOGICAL TESTS

Test		June 1985	Nov. 1985	Aug. 1986	March 1988
Paired associates	Learning	43/3	45/5	49/9	51/12
	retention	53/16**	41/2	55/16**	53/15
Visuospatial	Copying	47/10	51/15**	47/11	44/9
	learning	49/13**	49/13**	49/13**	43/9
	retention	47/10	44/7	49/12	47/12
	'total'	48/13	46/12	49/15	45/12
Digit span	Forward	51/6	45/1	45/1	38/-5
	backward	52/-8	32/-7	23/-16**	23/-14
Block design		38/-1	51/13	44/6	36/-1
Trails	A	45/6	50/12	55/17**	45/8
	B	31/-8	30/-8	29/-9	29/-8
Symbol digit modality test		44/8	36/0	41/5	38/4
Overall mean		39/5	37/4	40/7	34/2
		n.s.	n.s.	n.s.	n.s.

*Raw test scores were made comparable by conversion to standard test scores (mean = 50, SD 10 in 120 normal subjects aged 20-73 yrs). An expected score was computer based on regression equations (derived in analysis of the normal subject sample) with age and education, as the regressed variables. Difference scores represent the mean differences (residuals) between the expected and the actually observed scores. The observed score (numerator) and the difference between expected and observed score (denominator) are given above. **The difference is significantly different from zero ($P < 0.05$): n.s. = not significant.

error. Comprehension of words and sentences was normal (Peabody score 18/18 and Token Test 35/36, respectively). Calculation was preserved. There was no buccolingual apraxia. No intellectual impairment was demonstrable by a standardized psychological battery as compared with a control group of comparable age and education (Table 1, where the test results of auditory memory span, verbal learning and memory, visuospatial copying, learning and memory, visuospatial ability and visuomotor speed are presented).

The patient was re-examined regularly over 3 yrs by the same test battery. Oral aphasia testing was recorded on magnetic tape. After 6 months, the articulation difficulties were somewhat more pronounced, and spontaneous speech had developed a staccato rhythm. The aphasic deficits were unchanged. Three yrs after onset, articulation deficits and tremor of the voice sometimes made her utterances difficult to understand. Her oral language was often telegraphic and a slight buccofacial apraxia was also noted. Four yrs after onset, the patient's voice had developed a pronounced vibrating tremor and articulation was almost impossible. Most verbal functions previously assessed could not be evaluated orally at this time but naming was found to be normal when the patient was allowed to write her answers. For the first time, however, there was slight impairment in comprehension, with a Token Test result of 28/36. Calculation skills were still preserved and the patient remained intellectually unimpaired, with a Wechsler performance IQ of 103. The various psychometric scores and their progression are summarized in Table 1.

During the 3 yrs of her follow-up, 4 CT scans were performed (Siemens Somatom), 2 with contrast enhancement. They were all considered normal showing neither focal lesions nor atrophy. Magnetic resonance imaging (MRI) (Siemens Magnetom, 1.5 tesla), performed 2 yrs after onset, revealed confluent periventricular hyperdensities as well as multiple irregular and sharply demarcated lesions of increased intensity in adjacent areas of white matter, including the subcortical part of the perisylvian regions. Moreover, slight atrophy of the left perisylvian region was noted (fig. 1). Repeat MRI examination performed 4 yrs later did not demonstrate any progression.

Doppler ultrasound examinations of the neck vessels were normal. The CSF was normal, including protein electrophoresis. Repeated EEGs were normal. Multiple somatosensory and auditory evoked potentials remained normal, whereas visual evoked potentials (VEPs), initially normal, later showed a 20% lengthening of the latency of the positive potential P93 with patterned stimulation.

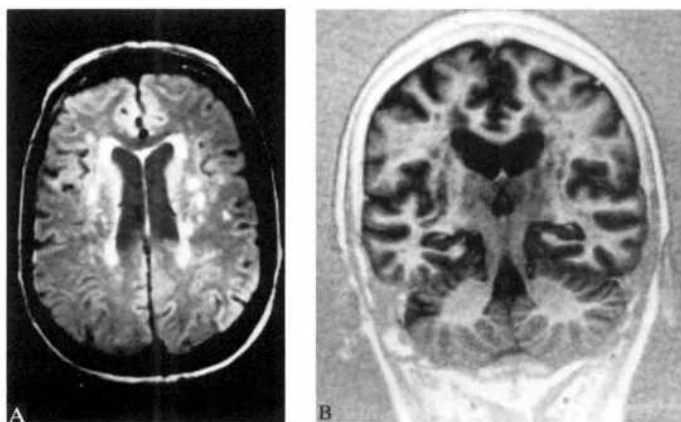


FIG. 1. MRI 2 yrs after onset of disease. White matter lesions are prominent, as demonstrated by the spin echo technique (TR/TI = 1800/28 ms) (A), and an inversion recovery pulse sequence (TR/TI = 2450/400 ms) (B). Re-examination 2 yrs later revealed no further changes.

METHODS

Dynamic ¹³³xenon inhalation SPECT

Regional cerebral blood flow (rCBF) was first assessed using ¹³³xenon inhalation and a rapidly rotating single photon emission tomograph (Tomomatic 64, Medimatic, Copenhagen). A complete study takes 4.5

min, during which 80 mCi of ^{133}Xe in a 4 l mixture of air and oxygen were inhaled in a closed circuit. Three transaxial brain slices were studied simultaneously. End-tidal pCO_2 was monitored by means of an infrared capnograph. The arterial cerebral input was estimated from the lung activity curve obtained by placing a narrowly collimated detector over the apex of the right lung. An algorithm based on a combination of sequential tomography and the early picture method and the time-activity lung curve, allowed the calculation of mean and rCBF (Kanno and Lassen, 1979; Celis *et al.*, 1981). We thus obtained average flow maps where mean rCBF values were calculated as the mean flow within mirrored regions of interest depicting the cerebral hemispheres, the cerebellar hemispheres, the basal ganglia, the frontal, temporal, parietal and occipital lobes. After this first study, the patient was repositioned 2 cm lower and a second study was performed in order to obtain 6 flow maps per examination. The data thus obtained were compared with those of age-matched controls (Shirahata *et al.*, 1985; Vorstrup, 1988). A side-to-side asymmetry exceeding 8% CBF was also measured before and after the administration of 1 g of acetazolamide, a potent cerebral vasodilator (Vorstrup *et al.*, 1984).

HMPAO SPECT

Technetium-99m HMPAO was prepared by adding 35 mCi of sodium pertechnetate Tc-99m in 5 ml of sterile eluate from a standard $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator to a unit dose kit. The patient then received 30 mCi of the Tc-99m labelled HMPAO in 8 ml of saline as an i.v. bolus in the antecubital fossa within 20 min of its preparation. Imaging was performed by the tomograph previously described using a high resolution collimator. The patient was first placed so that the set of 3 brain slices studied would be located 1 cm, 5 cm, and 9 cm above the orbitomeatal (OM) line. After an acquisition period of about 25 min, the patient was repositioned 1.3 cm and finally 2.6 cm lower, when the flow study was simultaneously repeated. We thus obtained 9 different horizontal images of flow distribution. Correction for technetium 99m time-decay was applied, as well as the correcting algorithm of Lassen *et al.* (1988), using the left cerebellar hemisphere as the internal standard. Regional blood flow values relative to the cerebellar count-rate were then determined within the outlines of the same period regions of interest previously described. All studies were performed in a quiet room with the patient's eyes open and ears unoccluded.

RESULTS

One year after onset, CBF was significantly lower in the inferior frontal and temporal areas at rest. The response to acetazolamide was normal. Two years after onset, ^{133}Xe CBF tomography showed a significant left temporal hypoperfusion accompanied by a large reduction in the ipsilateral hemisphere, which predominated in the frontal and anterior parietal territories. The frontal parts of the right cerebral hemisphere were also slightly affected 1 yr after onset of symptoms. The corresponding absolute rCBF values are summarized for the patient and for 5 normal volunteers aged 76 (71–79) yrs in Table 2. A CO_2 correction by 3%/mmHg to a PaCO_2 of 38 mmHg was applied to make this comparison possible.

Simultaneous high resolution CBF imaging by HMPAO SPECT also demonstrated a well circumscribed decreased flow in the left temporal lobe, with parallel flow decrease in the ipsilateral parietal and frontal cortex and no crossed cerebellar diaschisis. Four years after onset the same pattern was seen, but with an extension of the hypoperfused region towards the nondominant frontal lobe, in both HMPAO (fig. 2) and ^{133}Xe inhalation studies (fig. 3).

DISCUSSION

The slowly progressive language impairment of our patient would certainly suggest a diagnosis of primary progressive aphasia (PPA) as defined by Mesulam (1987), although

TABLE 2. THE ABSOLUTE rCBF VALUES OBTAINED BY $^{133}\text{XENON}$ COMPARED WITH CONTROLS** AND Tc99m-HMPAO DISTRIBUTION

Cerebral blood flow $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$								
Region	Patient						Controls*	
	May 1985		Sept. 1986		Sept. 1988		Left	Right
	Left	Right	Left	Right	Left	Right		
Hemispheres	51	54	51	55	51	54	57/3	58/3
Cerebellum	d51	50d	d53	51d	d51	49d	59/2	59/3
Middle frontal	d46	52	d43	49	d43	48d	54/3	57/4
Lower frontal	d44	47d	d45	48	d39	44d	54/3	56/4
Upper frontal	d46	49d	d45	48d	d39	42d	58/4	60/4
Broca	56	62	d51	61	d47	52	62/4	61/3
Sylvian cortex	58	60	d53	61	d53	59	61/3	61/3
Basal ganglia	56	60	56	57	59	59	60/4	61/3
Temporoparietal	49	50	48	51	48	48	51/3	52/3
Lower parietal	50	50	49	52	49	51	53/4	54/4
Upper parietal	54	57	53	58	55	60	59/3	61/4
Wernicke	56	57	54	60	d53	57	60/3	61/4
Occipital	55	59	61	61	58	59	61/3	61/4

Patient's Tc99m-HMPAO activity in 1988**

Region	Left	Right
Hemispheres	47	50
Cerebellum	51	55
Middle frontal	45	50
Lower frontal	48	48
Upper frontal	39	41
Broca	39	45
Sylvian cortex	51	53
Basal ganglia	55	56
Temporoparietal	48	49
Lower parietal	49	50
Upper parietal	53	53
Wernicke	51	52
Occipital	63	64

Underlined figures = side-to-side asymmetry ratio significantly abnormal ($\geq 9\%$) (Vorstrup, 1988). d = decreased rCBF compared with controls (lower than mean - 2 SD). * Five normal volunteers as described in the text; means/SD are shown. ** Data corrected for back diffusion and normalized to cerebellum = $51 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ according to the algorithm of Lassen *et al.*, 1988.

some aspects were quite unusual. Disturbances of repetition, dysprosody and fluency gave resemblances to Broca's aphasia and PPA, but the absence of any significant naming or grammatical impairment would be unusual in both (Benson and Geschwind, 1985; Mesulam, 1987). The early appearance of what was rapidly to become a crippling articulatory disturbance with virtual anarthria (Schiff *et al.*, 1983) was atypical of PPA, the aphasic type of Alzheimer's (Mesulam, 1987) or Pick's disease, and even of vascular aphasia (Benson and Geschwind, 1985). Functionally, this pattern suggested a very focal lesion, and the clinical diagnosis could only be of selective and progressive pathology of the cortex (and perhaps the subcortex) of the left frontal opercular region (Benson and Geschwind, 1985). Neuroradiological investigation has left the diagnosis unresolved, as the only neuroradiological finding of clinical relevance was slight atrophy of the left

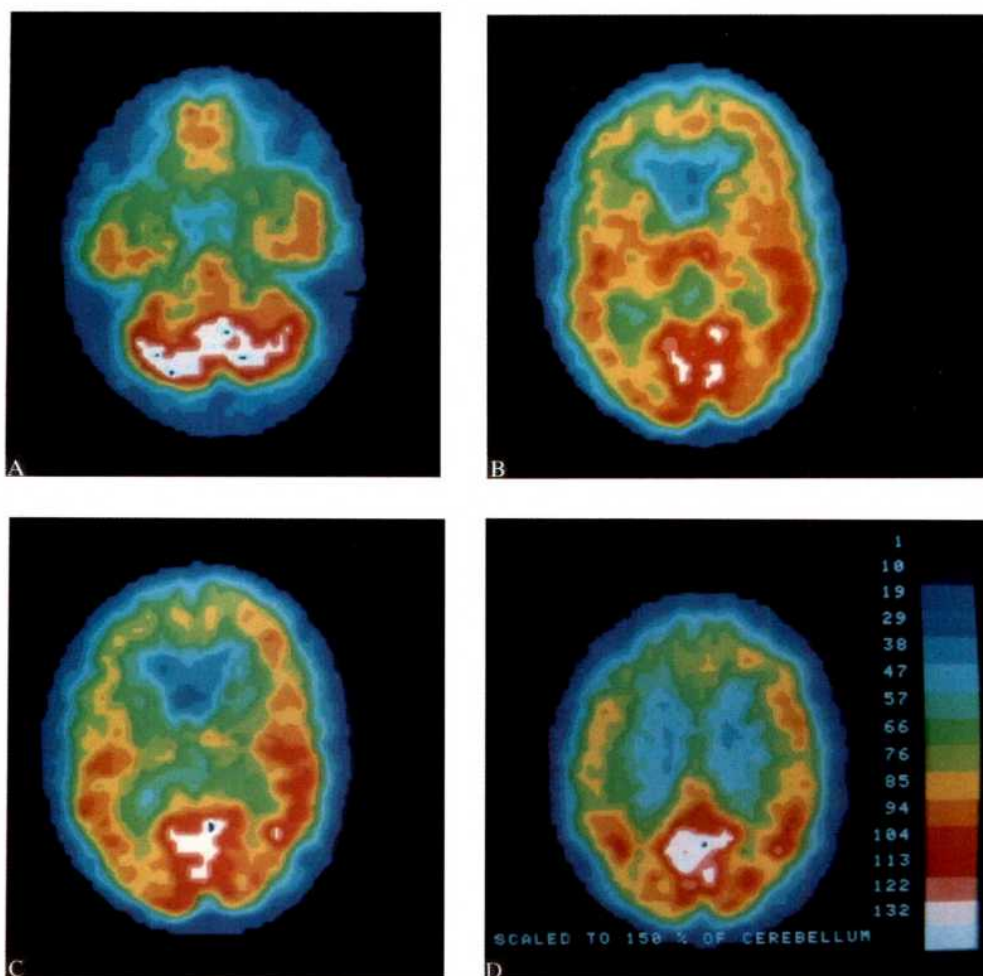


FIG. 2. SPECT study of rCBF using Tc99m-d,l-HMPAO, September 1988. The HMPAO distribution data have been corrected for back diffusion of tracer by the algorithm of Lassen *et al.* (1988). In the horizontal plane situated 2.3 cm above the orbitomeatal plane (OM + 2.3 cm) (A), the temporal poles have lower medial activity on the left side. No crossed cerebellar diaschisis is seen. In the OM + 4 cm plane (B), the left frontal and temporoparietal rCBF is lower than on the right side. This becomes more evident at the higher brain sections situated at the OM + 5 cm (C) and OM + 6.3 cm (D) levels. The colour-coded scale is indicated on (D). The image is scaled to cerebellum = 100%.

perisylvian region on MRI. The MRI findings of multiple white matter lesions were of interest, although their anatomical location did not correlate with the clinical symptoms. Their significance in a patient of this age is uncertain. They have been described in multiple sclerosis, cerebral small vessel disease, Alzheimer's disease, hydrocephalus, systemic hypertension, diabetes and normal ageing (Goto *et al.*, 1981; Pullicino *et al.*, 1983; Kirkpatrick and Hayman, 1987; Brust, 1988; Kertesz *et al.*, 1988). The VEP finding of a slightly (20%) prolonged P93 is in agreement with the MRI changes and more in keeping with white matter disease than a cortical process.

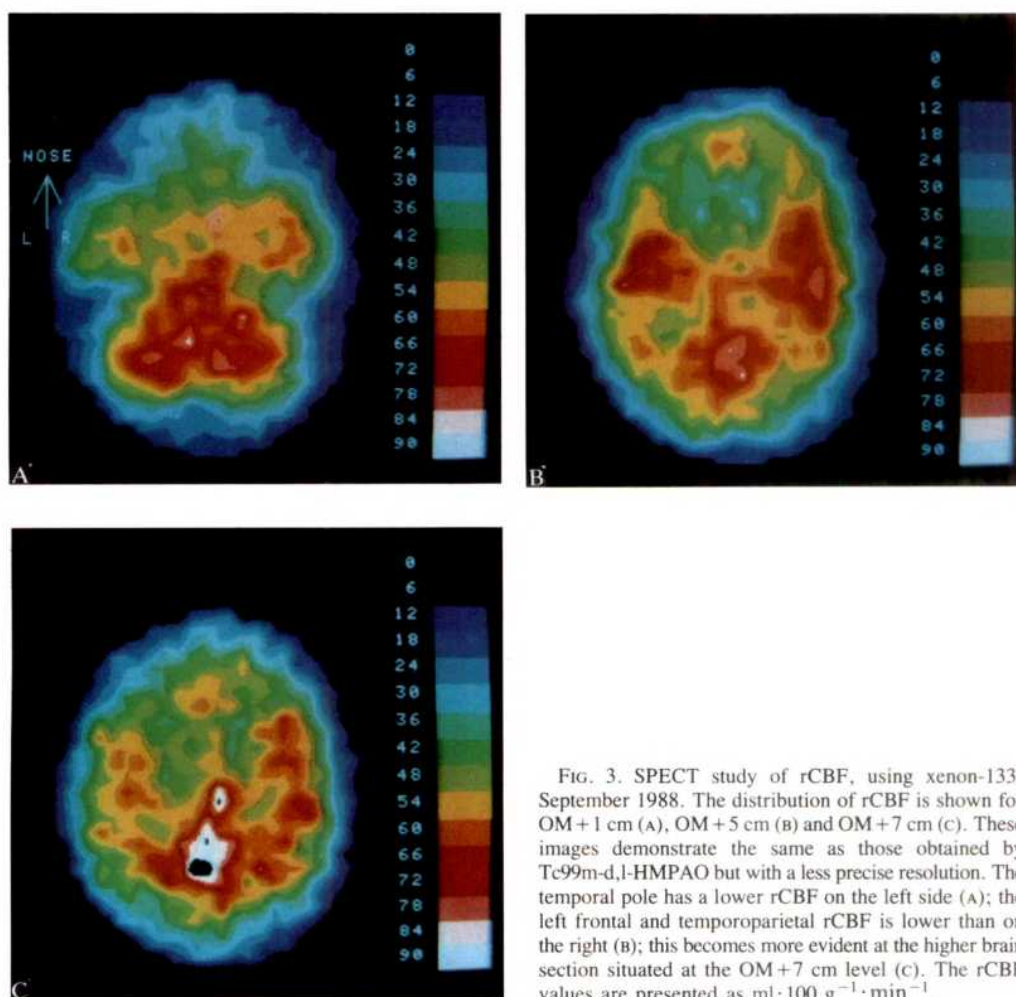


FIG. 3. SPECT study of rCBF, using xenon-133, September 1988. The distribution of rCBF is shown for OM + 1 cm (A), OM + 5 cm (B) and OM + 7 cm (C). These images demonstrate the same as those obtained by Tc99m-d,l-HMPAO but with a less precise resolution. The temporal pole has a lower rCBF on the left side (A); the left frontal and temporoparietal rCBF is lower than on the right (B); this becomes more evident at the higher brain section situated at the OM + 7 cm level (C). The rCBF values are presented as $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.

In great contrast, however, were the striking abnormalities seen on the SPECT blood flow studies. This is the first reported case of primary progressive aphasia, in which evidence of more widespread involvement was revealed by CBF studies, before any alterations emerged in intellectual psychometric tests. The initial blood flow asymmetry implicating the left lower frontal and temporal regions presumably located the primary lesion. The later images showing flow decreases in a much wider area comprising the ipsilateral frontal and parietal cortex, extending to the contralateral frontal cortex, documented an insidious evolution from a focal lesion towards a widespread, bilateral degeneration. Only a long-term follow-up will be able to determine whether this vast subclinical injury is a precursor of dementia, though the recent lengthening of the VEPs seems to suggest the beginning of more extensive clinical deficits.

Not only the asymmetry ratio but also the absolute CO_2 -corrected rCBF values were decreased in the affected frontal lobe. The rCBF of the opposite (right) frontal lobe

was also slightly decreased. Comparison of the absolute rCBF values with the data obtained in the small control group of 5 age-matched normal volunteers was based on a CO₂-correction step. Because of this and scattered radiation in the images, the order of magnitude of the 'true' regional flow decrease in this patient is only roughly estimated by the present method. The changes are, however, significant. The patient was studied by two different flow-tracers to exclude the possibility that the asymmetric decrease of rCBF was due to an artefact of one of the radiopharmaceuticals. The same blood flow distribution was found using both methods (Table 2).

Although CBF or metabolic studies in progressive aphasia are rare, this pattern is unique. Chawluk *et al.* (1986) studied the glucose metabolism of 2 patients with progressive aphasia without dementia: 1 patient had a metabolic decrease of the left temporal lobe, and the other of the parieto-occipital junction. Poeck and Luzzatti (1988) described a case of progressive aphasia with developing dementia studied by HMPAO SPECT. They reported a flow decrease of 13% in the left hemisphere, centred on the temporo-occipital region. Similarly, Celsis *et al.* (1987) studied rCBF in patients with 'dementia of the Alzheimer type' with aphasia as the presenting symptom. Using ¹³³xenon and SPECT they showed focal defects, with an occasional diffuse cerebral decrease, though all studies were performed at a time when the patients were considered to be clinically demented.

In the present case, PPA, as defined by a focal lesion due to spongiform degeneration, seemed to be eliminated by the SPECT flow studies. The extensive hemisphere hypoperfusion could not be attributed to a form of intrahemispheric diaschisis such as that seen in ischaemic focal lesions of the internal capsule (Takano *et al.*, 1985; Pappata *et al.*, 1987) or the thalamus (Baron *et al.*, 1986) because of its nonvascular and bilateral disposition. The SPECT findings could in our opinion most convincingly be explained by a chronic progressive pathology of the brain tissue itself. A probable differential diagnosis must include the primary degenerative dementias and frontal lobe degeneration of non-Alzheimer type (Brun, 1987; Neary *et al.*, 1987), although the pattern of linguistic deterioration was quite incompatible with either diagnosis. The absence of any dementia in this patient's well documented family history excludes the diagnosis of familial dysphasic dementia (Morris *et al.*, 1984). The absence of marked cerebral atrophy on CT scan and MRI makes the syndrome of 'nonfamilial dysphasic dementia', described by Mehler *et al.* (1987) as characterized by reduced cortical somatostatin-like immunoreactivity improbable, although their hypothesis of dementia due to intrinsic cortical degeneration is intriguing. Progressive subcortical gliosis of Neumann (Neumann and Cohn, 1967; Verity and Wechsler, 1987) might better fit these differing aspects, as would a form of Creutzfeld-Jacob disease of long duration (Brown *et al.*, 1984).

In conclusion, in this case the progressive phasic impairment without dementia, the SPECT flow studies clearly demonstrated extensive cerebral involvement, in major discrepancy with very focal clinical features and normal intellectual psychometric testing. Obviously more sensitive than CT or MRI, these images suggested the existence of diffuse cerebral degeneration instead of primary progressive aphasia. We believe that SPECT flow imaging should be used in the difficult differential diagnosis of degenerative diseases with focal clinical onset, especially in patients with normal or diffusely abnormal structural tomography (CT and MRI) of the brain although only long-term follow-up and pathological analysis can give us the final diagnosis.

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CORTICAL AND SUBCORTICAL GLUCOSE CONSUMPTION MEASURED BY PET IN PATIENTS WITH HUNTINGTON'S DISEASE

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SUMMARY

In 23 patients with moderate to severe Huntington's disease (HD) and 21 normal volunteers, the regional cerebral metabolic rate of glucose consumption (rCMRGlc) was measured in the cerebellum, thalamus, striatum, and cortex using positron emission tomography and the ¹⁸F-deoxyglucose method. In contrast to previous reports, rCMRGlc was reduced not only in the striatum, but also in the cerebral cortex of patients with HD as compared with normal subjects. No significant difference between HD patients and normal subjects was found for thalamic and cerebellar rCMRGlc. To investigate the relationship between the clinical status and rCMRGlc, correlation coefficients for the clinical data were calculated for absolute values of rCMRGlc and for cerebellar ratios (CR) of rCMRGlc. The duration of chorea correlated significantly only with the absolute values of frontoparietal and temporo-occipital rCMRGlc and with the CRs of most cortical regions evaluated. The severity of chorea correlated significantly only with lentiform nucleus rCMRGlc. The severity of dementia correlated significantly only with the frontoparietal and temporo-occipital rCMRGlc, the CRs of most cortical regions, and the CR for the caudate nucleus. The degree of disability correlated significantly with the CRs of all regions evaluated except the occipital and the superior frontal cortex. It appears from this study that there is a reduction not only for the striatum but also for cortical rCMRGlc in patients with manifest HD, and that the cortical reduction of rCMRGlc contributes to the severity of clinical symptoms in these patients. This challenges the concept that dementia in HD is of purely subcortical origin.

INTRODUCTION

Huntington's disease (HD) is a rare disorder characterized by autosomal dominant inheritance, chorea and progressive dementia (for a review, *see* Martin and Gusella, 1986; Penney and Young, 1988). As a clinical entity it was first described by Huntington in 1872. At the end of the nineteenth century, two publications independently showed that gross degeneration occurs in the striatum of HD patients (Anton, 1896; Lannois and Paviot, 1897). Since then, numerous reports investigating the neuropathological substrate of HD have been published (for references, *see* McCaughey, 1961; Lange *et al.*, 1976; Vonsattel *et al.*, 1985). In all these, degeneration of the striatum has been described as the most pronounced and typical change in HD. Some authors, however, have clearly stated that, in addition to striatal degeneration, degenerative changes can be found

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in the cerebral cortex (Alzheimer, 1911; McCaughey, 1961; Lange, 1981). Studies using computerized x-ray tomography (CT) have lent further support to the hypothesis that moderate cortical atrophy can accompany the more pronounced striatal changes in HD (Sax and Menzer, 1977; Terrence *et al.*, 1977; Oepen and Ostertag, 1981; Lange and Aulich, 1986). As cortical involvement in HD is not as pronounced as that of the striatum, and as cortical degeneration has been reported to vary markedly (McCaughy, 1961), its relevance in HD has been questioned (Penney and Young, 1988) and little investigated.

With the advent of positron emission tomography (PET) several authors have measured the regional cerebral metabolic rates for glucose (rCMRGlc) and oxygen (rCMRO₂) in HD (Kuhl *et al.*, 1982, 1984a; Garnett *et al.*, 1984; Hayden *et al.*, 1986, 1987; Leenders *et al.*, 1986; Young *et al.*, 1986; Hosokawa *et al.*, 1987; Mazziotta *et al.*, 1987; De Volder *et al.*, 1988). Some of these studies have focused on the clinically important issue of early diagnosis of HD and have shown that hypometabolism in the caudate nucleus precedes the onset of clinically overt chorea in persons at risk of HD (Hayden *et al.*, 1986, 1987; Mazziotta *et al.*, 1987). All studies on patients with manifest HD have demonstrated prominent decreases of striatal rCMRGlc and rCMRO₂, in agreement with the above-cited neuropathological and CT studies.

So far, only scarce and controversial evidence has existed concerning cortical energy metabolism in HD. Kuhl *et al.* (1982, 1984a) did not find a significant decrease of cortical rCMRGlc in their group of 13 patients, although they observed a significant decrease of an anteroposterior ratio of cortical rCMRGlc in a subgroup of 5 patients with a disease duration of more than 6 yrs. Young *et al.* (1986) and Berent *et al.* (1988) stated that in their studies, mainly aimed at investigating the relationship between rCMRGlc and the severity of symptoms in HD, cortical rCMRGlc was normal in their group of 15 patients with early to midstage HD. They related the severity of symptoms exclusively to indices of striatal rCMRGlc. Leenders *et al.* (1986), however, reported a decrease in absolute values of cerebral blood flow, rCMRO₂, and rCMRGlc in the frontal cortex of 1 patient with HD. Recently, in a preliminary publication, we described a decrease of cortical rCMRGlc in a group of 13 patients with manifest HD and 5 patients at risk of HD with psychiatric symptoms (Kuwert *et al.*, 1989). This study reports measurements of rCMRGlc in 23 HD patients and 21 normal volunteers using a new-generation high resolution PET scanner. The aims of this study were to compare cortical and subcortical rCMRGlc in patients with manifest HD with the rCMRGlc of normal subjects, and to clarify further the relationship between rCMRGlc and clinical symptoms of this disease with special attention to cortical rCMRGlc.

SUBJECTS AND METHODS

Subjects

Twenty-three patients (mean age 42.7 ± 10 yrs; 12 males, 11 females) with manifest HD and 21 normal subjects (mean age 41.1 ± 12.5 yrs; 15 males, 6 females) entered the study. Both patients and normal subjects were scanned during the same period of time from October 1987 to November 1988. The blood glucose levels at the time of PET examination did not differ significantly between patients and control subjects (4.95 ± 0.67 vs 4.81 ± 0.63 mmol/l glucose). Written and informed consent was obtained from all subjects. The control group consisted of healthy volunteers. None of these individuals had a history of alcoholism, neurological disease, myocardial infarction, or diabetes mellitus and neurological examination was normal. All control subjects were not taking medications.

In the patient group, the diagnosis of manifest HD was made on the basis of a family history of HD and a clinical diagnosis of chorea. Blood tests were performed in these patients to exclude such other extra-pyramidal disorders as Wilson's disease and neuroacanthocytosis. Scales ranging from 0 (normal) to 3 (severely disturbed) were employed for grading the severity of clinical symptoms. The severity of chorea was assessed on a clinical rating scale with 0 indicating absence of chorea and 3 indicating the presence of constant or frequent gross choreiform movements (Lange *et al.*, 1983). The degree of dementia was determined using a score derived from a psychometric test battery. Psychometric testing included the vocabulary recognition test MWT-B (Merz *et al.*, 1975; Lehrl, 1977), an abbreviated German version of the WAIS (WIP; Dahl, 1972), a test of visuomotor performance (d2-test; Brickenkamp, 1972), a test measuring attention, concentration, general intelligence and cognitive flexibility (syndrome short test SKT; Erzickert, 1977), Benton's test (Benton, 1981), and a German version of Raven's matrices (Raven, 1938; Kratzmeier and Horn, 1980). All single test results were converted into scores ranging from 0 to 3. The average of these scores was defined as the overall degree of dementia. The degree of disability was rated analogously to the Shoulson-Fahn scale (Shoulson and Fahn, 1979; Lange *et al.*, 1983) according to the patients' ability to cope with everyday tasks. Although it was not the aim of this study to correlate rCMRGlc with the type and severity of psychiatric symptoms encountered in HD, it is evident that the presence of severe psychiatric symptoms such as psychosis or depression greatly influences the patient's ability to cope with everyday tasks and that the impact of these symptoms on the patient's condition is also evaluated by the above-described scale.

Table I shows detailed clinical data on the HD patients in this study. The duration of chorea in these patients ranged from 1 to 15 yrs with a mean duration of 6.1 ± 4.1 yrs. The mean severity of chorea was 1.5 ± 0.6 , the mean severity of dementia 1.6 ± 0.9 , and the mean disability severity 1.4 ± 0.8 . Thus patients with both mild and advanced disease were included in this study.

TABLE I CLINICAL AND X-RAY CT DATA IN THE GROUP OF PATIENTS WITH HUNTINGTON'S DISEASE

Case	Age (yrs)	Sex	DUR (yrs)	CHOR	DEM	DIS	Drugs	CC/OT	Atrophy
1 (A.B.)	36	M	6	1.5	2.0	1.7	BZ,BA	0.21	1.8
2 (S.B.)	41	F	4	1.5	2.0	1.8	0	0.21	1.5
3 (H.B.)	56	F	7	2.0	1.9	1.4	BA	0.3	1.8
4 (D.B.)	48	F	15	1.5	2.8	2.9	0	0.3	2
5 (M.E.)	31	M	2	2.0	1.1	2.0	PH,BU	0.15	1.2
6 (W.F.)	32	M	1	1.0	0.4	0.4	0	0.14	0.8
7 (K.G.)	35	M	8	0.5	1.7	1.0	BZ	0.1	0
8 (R.H.)	46	F	8	2.0	2.6	1.8	BA	0.18	1
9 (A.K.)	47	M	5	1.5	1.0	0.5	0	0.16	1.3
10 (F.K.)	31	M	5	2.0	1.8	2.0	PH,BU,BZ	0.13	0
11 (U.K.)	46	F	5	1.5	2.5	1.8	BA	0.19	1.8
12 (A.L.)	45	M	1	1.0	2.6	2.0	BA	0.16	1.7
13 (I.M.)	54	F	1	1.0	0.6	0.2	0	0.17	1.5
14 (E.M.)	60	F	10	2.0	2.5	2.4	PH,BU,BA	0.19	1.5
15 (I.O.)	47	F	5	1.0	0.4	0.2	0	0.15	1.2
16 (H.P.)	42	M	10	1.5	2.1	1.0	0	0.18	1.7
17 (G.P.)	33	F	8	1.5	0.7	0.7	0	0.1	1.2
18 (Hc.P.)	53	F	15	2.5	2.3	2.0	PH	0.19	1.7
19 (K.S.)	32	M	1	0.5	0.2	0.7	0	0.12	1
20 (H.S.)	35	M	5	2.5	1.6	1.0	0	0.14	2
21 (W.S.)	62	M	1	0.5	0	0.7	0	0.13	0.8
22 (G.S.)	27	M	9	2.0	1.0	1.3	0	0.12	1
23 (A.W.)	42	F	9	1.5	2.4	2.0	BZ,PH	0.16	1.7

DUR = duration of chorea; CHOR = severity of chorea; DEM = severity of dementia; DIS = degree of disability; BZ = benzodiazepines, PH = phenothiazines, BU = butyrophenones, BA = substituted benzamides (sulpride or tiapride); CC/OT = shortest distance between caudate heads/distance between the outer tables of the skull at the CC line, atrophy = cortical atrophy evaluated on CT.

In all patients CT was performed using a CGR ND 8000 head scanner in the same year as the PET study. The control subjects did not have a CT scan. The CT scans were evaluated by a neuroradiologist (A.A.) independently of the clinical and PET data. In order to evaluate caudate atrophy the intercaudate distance (CC) and the distance between the outer tables of the skull (OT) along the CC line were measured (Stober *et al.*, 1984). An index of caudate atrophy was calculated by dividing CC by OT. The mean CC/OT was 0.17 ± 0.05 , indicative of caudate atrophy and comparing well with published results for symptomatic HD patients (Stober *et al.*, 1984). Cortical atrophy was evaluated by measuring the width of the three widest sulci in the frontal, parietal, and occipital cortex. Cortical atrophy was then graded from 0 (mean sulcal width < 2 mm) to 3 (mean sulcal width > 5 mm) as reported elsewhere (Lange and Aulich, 1986). The average degree of cortical atrophy thus evaluated was 1.3 ± 0.6 , the degree of parietal atrophy 1.4 ± 0.6 . Although no age-matched control group was available for the CT scans, it was concluded that the indices of cortical atrophy given above indicate moderate cortical atrophy in view of the relatively young age of the patients and the fact that postmortem examinations of normal cadavers revealed that no atrophy of the parietal cortex occurs before the age of 60 yrs (Eggers *et al.*, 1984). This interpretation is in good agreement with previous CT studies reporting on moderate cortical atrophy in patients with manifest HD (Sax and Manzer, 1977; Terrence *et al.*, 1977; Oepen and Osterag, 1981).

Twelve of the 23 HD patients were not receiving medication and 11 were medicated as listed in Table 1. No patient was sedated for the purpose of this study. All patients of this group had refrained from using alcohol at least 1 yr before the PET study.

Positron emission tomography

PET scanning was performed using the Scanditronix PET PC-4096 with a maximal spatial resolution of 4.8 mm in the centre of the field of view and 6 mm in the z axis (full width at half maximum; FWHM). Images were reconstituted by filtered back-projection using a filter width of 5 mm leading to an actual resolution of 7.1 mm in the x and y axes and of 6 mm in the z axis (FWHM). Attenuation-correction was performed using $^{68}\text{Ga}/^{68}\text{Ge}$ derived transmission scans. The scanning took place in a quiet and dimly lit room, with the subject's eyes open and his ears unplugged. Arterialized blood was drawn through a fine-gauge intravenous cannula. ^{18}F -fluoro-deoxyglucose (FDG) was provided by the Institute of Nuclear Chemistry of the KFA Jülich and synthesized according to the procedure of Hamacher *et al.* (1986), which avoids contamination of FDG with ^{18}F -fluoro-deoxymannose. Cerebral glucose consumption was measured after injection of 5–8 mCi FDG (185–296 MBq) according to the standard procedure described by Reivich *et al.* (1979). rCMRGlc was calculated according to the standard procedure described by Reivich *et al.* (1979) using Sokoloff's model equation (Sokoloff *et al.*, 1977), the kinetic rate constants published by Reivich *et al.* (1985) and a lumped constant of 0.52 (Reivich *et al.*, 1985). In each subject rCMRGlc was measured in 15 orbitomeatal parallel slices (OM slices) simultaneously. The most inferior OM slice was 2.5 cm above the orbitomeatal line.

Data analysis

In order to evaluate cerebellar, thalamic, and cortical rCMRGlc, 21 regions of interest (ROI) were drawn manually by an examiner blind to diagnosis and symptoms of the examined subject (*see fig. 1*). Using a range-setting program provided by the manufacturer of the PET machine, the lowest 20% of the rCMRGlc values were not displayed on the screen allowing the partial volume effect to be minimized by drawing the ROIs close to the peak rCMRGlc of each structure evaluated. The cerebellar, thalamic, and cortical ROIs were identified by comparing the OM-parallel PET slices with anatomical sections of horizontal brain slices (Duara *et al.*, 1983) displayed in a neuroanatomical atlas (Talairach and Tournoux, 1988); the horizontal slices in this atlas can be considered approximately parallel to the OM plane (Szikla *et al.*, 1977). This method takes into account the fact that PET slices obtained at identical levels above an externally defined OM line do not always include corresponding brain regions due to considerable variation between individuals in the size and shape of the head and brain (Talairach and Tournoux, 1988; Duara *et al.*, 1983). As the identification of a single gyrus was thought to be difficult in patients with cortical atrophy, cortical ROIs encompassed several adjacent gyri as described below.

Cortical ROIs were placed on the three following OM-parallel slices. (1) An OM slice corresponding to slice 10 of Talairach's atlas (*see fig. 1a*). On this slice 2 cortical ROIs were drawn on each hemisphere: (a) one on the inferior frontal cortex encompassing the lower parts of the superior, medial and inferior frontal gyri; (b) a second on the inferior (and lateral) temporal cortex encompassing parts of the superior,

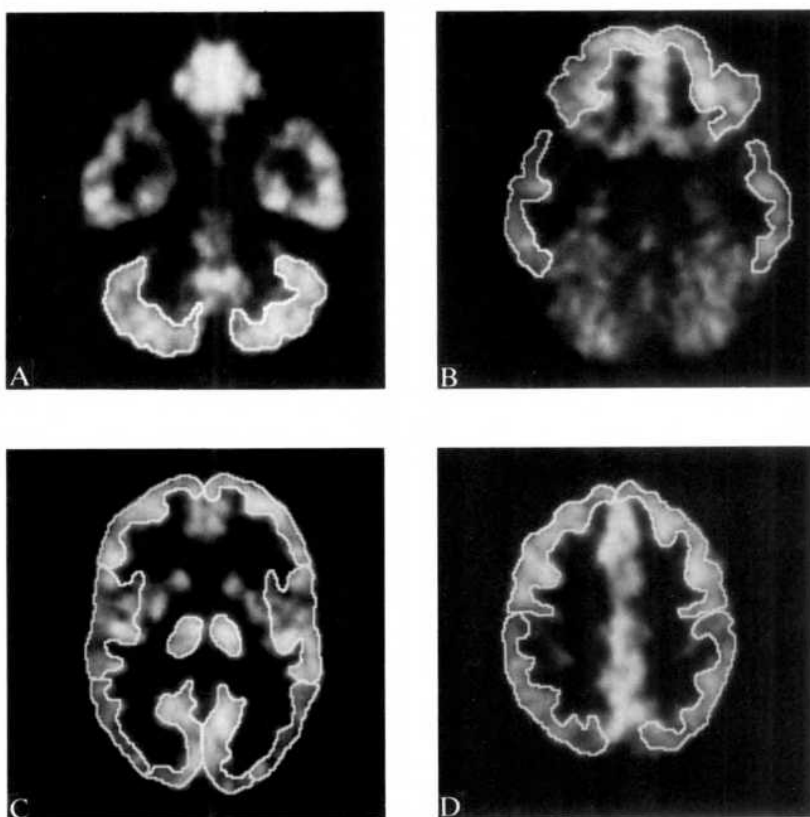


FIG. 1. Regions of interest drawn on orbitomeatal parallel PET slices of rCMRGlc in a normal subject (for description, *see text*).

medial and inferior temporal gyri. (2) An OM slice corresponding to slice 7_8 of Talairach's atlas. On this slice 4 cortical ROIs were drawn on each hemisphere (*see fig. 1c*): (a) one on the intermediate frontal cortex including parts of the superior, medial and inferior frontal gyri; (b) a second on the frontoparietal cortex including parts of the frontoparietal operculum, the insular cortex and a small part of the superior temporal gyrus; (c) a third on the temporo-occipital cortex including parts of the superior and medial temporal gyri, and parts of the medial occipital gyrus; (d) a fourth on the occipital cortex including parts of the medial occipital gyrus, the cuneus and the striate area. (3) An OM slice corresponding to slice 4 of Talairach's atlas. On this slice 2 cortical ROIs were drawn on each hemisphere (*see fig. 1d*): (a) 1 ROI on the superior frontal cortex corresponding approximately to the anterior half of the cortical rim displayed on this slice; (b) 1 ROI on the superior parietal cortex corresponding approximately to the posterior half of the cortical rim displayed on this slice.

Thalamic rCMRGlc was measured by placing a ROI on the thalamus displayed on the PET slice corresponding to Talairach's slices 7_8 (*see fig. 1c*). Cerebellar rCMRGlc was evaluated by placing a ROI on the convolutions of the cerebellar cortex on the PET scan corresponding to Talairach's slices 10_11 (*see fig. 1a*).

An additional ROI comprised the whole brain slice on the OM slice corresponding to Talairach's slices 7_8. Its size can be taken as a relative estimate of the size of the whole brain (Hatazawa *et al.*, 1987a).

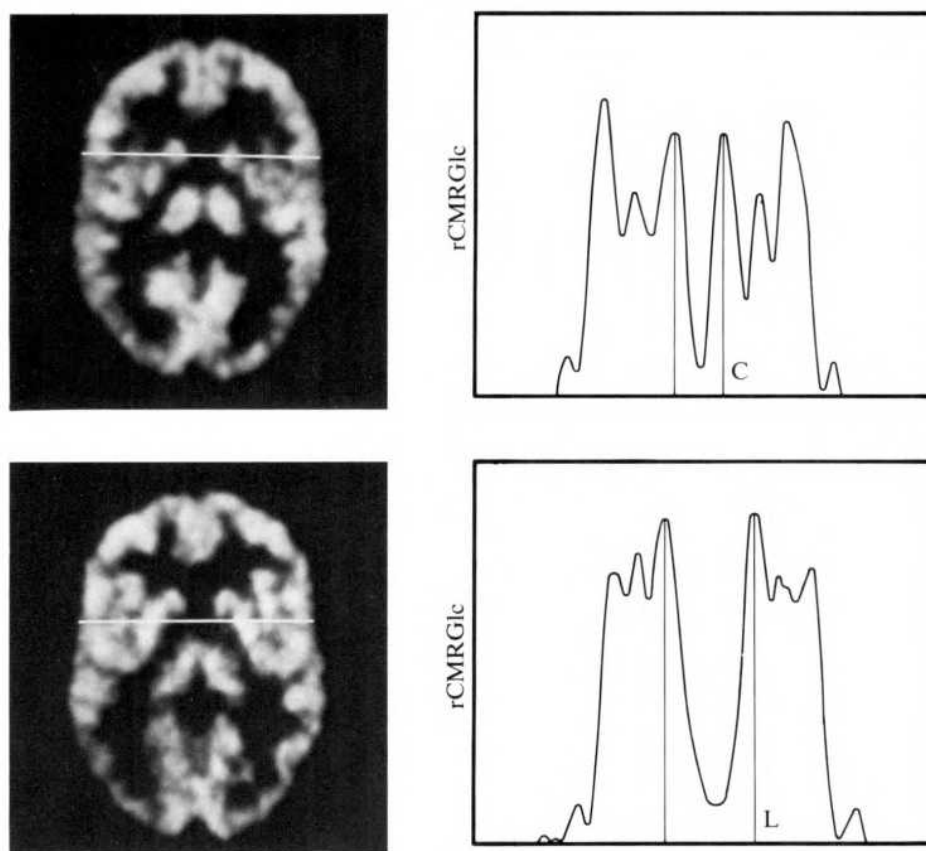


FIG. 2. Cross-sectional histograms were obtained through the caudate heads (*upper*) and through the lentiform nuclei (*lower*), allowing the measurement of caudate (C) and lentiform rCMRGlc (L) (Young *et al.*, 1986).

In addition to the values of rCMRGlc, the ROI sizes were provided by the ROI software of the PET manufacturer. The total cortical ROI area was calculated as the sum of all cortical ROI sizes.

Since in advanced HD, striatal rCMRGlc is low (Kuhl *et al.*, 1982) and the striatum grossly atrophic, visually-guided ROI measurements cannot be considered a precise method for measuring striatal rCMRGlc (Young *et al.*, 1986). In order to overcome this difficulty the method described by Young *et al.* was used to quantify caudate and lentiform rCMRGlc. The principle of this method is that peak values of rCMRGlc are measured on cross-sectional histograms (*see fig. 2*). Using differential range settings, the atrophic caudate nuclei in HD patients were identifiable visually in 21 of 23 cases; in the remaining 2 patients the cross-sectional histograms were placed 1 cm anterior to the anterior tip of the thalamus. The peak value of caudate rCMRGlc was then determined at the shoulder or inflection of the curve, as described by Young *et al.* (1986) and Berent *et al.* (1988). The peak value of the lentiform nucleus was determined analogously on a cross-sectional histogram placed 0.5 cm anterior to the thalamus on the OM-parallel slice corresponding to Talairach's slice 8.

The means of rCMRGlc in the left and right regions (weighted for their cross-sectional area for cortical, thalamic, and cerebellar ROIs) were calculated and used in the further analysis. The arithmetic mean of all cortical regions weighted for their cross-sectional area was calculated as an estimate of the mean cortical glucose consumption of each subject. In order to test Kuhl's hypothesis of hypofrontality in HD patients,

ratios were calculated between the weighted mean of all frontal regions (FRO) and the occipital cortex, between FRO and the weighted mean of the frontoparietal and the superior parietal cortex, and between FRO and the weighted mean of the inferior temporal and the temporo-occipital cortex.

In order to normalize the PET data, cerebellar ratios (CR) were calculated between the value of each region and the cerebellar rCMRGlc in each subject. In order to allow a comparison between this study and the studies by Young *et al.* (1986) and Berent *et al.* (1988), ratios between striatal rCMRGlc and mean cortical rCMRGlc were also calculated (cortical ratios). In addition to an analysis of correlation between the absolute values of rCMRGlc and the clinical data, these cerebellar and cortical ratios were used to correlate PET data with the severity of clinical symptoms because of the great variation of absolute values of rCMRGlc (Kuhl *et al.*, 1982; Tyler *et al.*, 1988).

Statistical analysis was performed using the statistical software package SAS (Statistical Analysis Systems). The difference of group means was tested using Student's *t* test after correction of the significance level using Bonferroni's correction for each sample. The correlation between PET data and clinical data was performed using Spearman's nonparametric rank correlation coefficients. The level of significance was set at $P < 0.05$.

RESULTS

The surface of the whole slice measured on the PET slice corresponding to Talairach's slices 7–8 was significantly smaller in HD patients than in normal subjects ($149 \pm 12.5 \text{ cm}^2$ vs $164 \pm 8.2 \text{ cm}^2$, $P < 0.01$, Student's *t* test). Cortical ROI sizes were smaller in HD patients than in control subjects (*see* Table 2); these differences were significant for parts of the frontal and the temporo-occipital cortex.

There was no significant correlation between the total cortical ROI area and rCMRGlc in normal subjects ($r = 0.25$, $P > 0.05$). In HD patients, the correlation coefficient between the total cortical ROI area and rCMRGlc was positive and significant ($r = 0.6$, $P < 0.01$) implying that in those patients in whom larger ROIs were drawn rCMRGlc tended to be higher. The total cortical ROI area correlated negatively with cortical atrophy as determined on CT scan ($r = -0.43$, $P < 0.05$). Mean cortical rCMRGlc correlated negatively with the degree of atrophy as determined on CT scan ($r = -0.58$, $P < 0.01$).

The mean cortical rCMRGlc was significantly reduced in HD patients (*see* Table 3), as was that of caudate and lentiform rCMRGlc. Thalamic rCMRGlc was approximately

TABLE 2 SIZES OF REGIONS OF INTEREST IN PATIENTS WITH HUNTINGTON'S DISEASE ($n = 23$) AND NORMAL SUBJECTS ($n = 21$)

	HD ROI size (cm^2)	Normal ROI size (cm^2)	P^2
Cerebellum	5.4 ± 0.8^1	5.6 ± 0.9	n.s. ³
Thalamus	2.3 ± 0.3	2.4 ± 0.4	n.s.
Inferior frontal cortex	5.9 ± 0.7	6.9 ± 0.9	$P < 0.01$
Intermediate frontal cortex	4.8 ± 0.6	5.7 ± 0.9	$P < 0.01$
Superior frontal cortex	9.0 ± 1.3	10.2 ± 1.5	n.s.
Inferior temporal cortex	4.7 ± 0.9	5.1 ± 1.2	n.s.
Temporo-occipital cortex	4.0 ± 0.8	5.0 ± 0.8	$P < 0.01$
Frontoparietal cortex	11.0 ± 2.0	12.7 ± 1.8	n.s.
Superior parietal cortex	9.3 ± 1.0	10.2 ± 1.5	n.s.
Occipital cortex	6.0 ± 0.8	6.4 ± 1.0	n.s.

¹ Mean $\pm$ SD, ² Two-tailed Student's *t* test using Bonferroni's correction, ³ Not significant ($P > 0.05$).

TABLE 3 MEAN CORTICAL, SUBCORTICAL AND CEREBELLAR rCMRGlc IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23) AND NORMAL SUBJECTS (n = 21)

	HD rCMRGlc ($\mu\text{mol}/100\text{ g/min}$)	Normal rCMRGlc ($\mu\text{mol}/100\text{ g/min}$)	P ²
Cerebellum	38.2 $\pm$ 6 ¹	40.3 $\pm$ 8	n.s. ³
Thalamus	44.5 $\pm$ 8.1	51.7 $\pm$ 10.6	n.s.
Caudate nucleus	21 $\pm$ 9.6	55.2 $\pm$ 10.3	P < 0.001
Lentiform nucleus	28 $\pm$ 12.2	63.7 $\pm$ 10.9	P < 0.001
Mean cortex	38.9 $\pm$ 6.6	46.8 $\pm$ 8.6	P < 0.01

¹ Mean $\pm$ SD; ² Two-tailed Student's t test using Bonferroni's correction; ³ Not significant (P > 0.05).

TABLE 4 CORTICAL rCMRGlc IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23) AND NORMAL SUBJECTS (n = 21)

	HD rCMRGlc ($\mu\text{mol}/100\text{ g/min}$)	Normal rCMRGlc ($\mu\text{mol}/100\text{ g/min}$)	P ²
Inferior frontal cortex	38.5 $\pm$ 6.4 ¹	47.6 $\pm$ 9.5	P < 0.01
Intermediate frontal cortex	39 $\pm$ 7.2	48.1 $\pm$ 9.9	P < 0.01
Superior frontal cortex	39.6 $\pm$ 8.2	48.7 $\pm$ 9.5	P < 0.02
Inferior temporal cortex	37 $\pm$ 7	43 $\pm$ 8.3	n.s. ³
Temporo-occipital cortex	36.3 $\pm$ 6.1	42.8 $\pm$ 7.5	P < 0.05
Frontoparietal cortex	38.3 $\pm$ 7.6	46.4 $\pm$ 8.7	P < 0.05
Superior parietal cortex	38.8 $\pm$ 6.6	45.1 $\pm$ 8	n.s.
Occipital cortex	45.5 $\pm$ 6.2	50.8 $\pm$ 9.4	n.s.

¹ Mean $\pm$ SD; ² Two-tailed Student's t test using Bonferroni's correction; ³ P > 0.05.

14% smaller in HD patients than in normal subjects; this difference, however, did not reach the required level of significance when Bonferroni's correction was applied. Cerebellar rCMRGlc was only about 5% smaller in HD patients than in normal subjects; the cerebellum thus seemed least affected in this group of HD patients. Significant differences between HD patients and normal subjects were found for rCMRGlc measured in all parts of the frontal cortex, the temporo-occipital cortex, and the frontoparietal cortex (see Table 4).

There was no significant difference in rCMRGlc of any brain region between the 12 unmedicated and the 11 medicated patients, implying that the mean cortical rCMRGlc measured in the unmedicated group (38.5 $\pm$ 7.3 $\mu\text{mol}/100\text{ g/min}$) also differed significantly from the mean cortical rCMRGlc measured in the control subjects (46.8 $\pm$ 8.6 $\mu\text{mol}/100\text{ g/min}$; P < 0.01 using the two-tailed Student's t test). This difference between HD patients and normal subjects was also found concerning rCMRGlc measured in the frontal regions: in the 12 unmedicated patients, rCMRGlc was 38.7 $\pm$ 7.2 $\mu\text{mol}/100\text{ g/min}$ in the inferior frontal cortex (compared with 47.6 $\pm$ 9.5 $\mu\text{mol}/100\text{ g/min}$ in the control subjects), 39.6 $\pm$ 8.6 $\mu\text{mol}/100\text{ g/min}$ in the intermediate frontal cortex (compared with 48.1 $\pm$ 9.9 $\mu\text{mol}/100\text{ g/min}$ in the control subjects), and 38.9 $\pm$ 8.5 $\mu\text{mol}/100\text{ g/min}$ in the superior frontal cortex (compared with 48.7 $\pm$ 9.5 $\mu\text{mol}/100\text{ g/min}$ in the normal subjects).

TABLE 5 CORRELATION OF CEREBELLAR, SUBCORTICAL, AND MEAN CORTICAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	<i>Duration of chorea</i>	<i>Severity of chorea</i>	<i>Severity of dementia</i>	<i>Degree of disability</i>
Cerebellum	0 ¹	0	0.08	0.26
Thalamus	-0.32	-0.3	-0.18	-0.08
Caudate nucleus	-0.11	-0.31	-0.3	-0.29
Lentiform nucleus	-0.35	-0.43*	-0.34	-0.37
Mean cortex	-0.34	-0.17	-0.3	-0.1

¹ Spearman's correlation coefficients; * $P < 0.05$.

TABLE 6 CORRELATION OF rCMRGlc IN DIFFERENT CORTICAL REGIONS WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	<i>Duration of chorea</i>	<i>Severity of chorea</i>	<i>Severity of dementia</i>	<i>Degree of disability</i>
Inferior frontal cortex	-0.31 ¹	-0.15	-0.25	-0.12
Intermediate frontal cortex	-0.33	-0.16	-0.32	-0.15
Superior frontal cortex	-0.35	-0.17	-0.26	-0.04
Inferior temporal cortex	-0.33	-0.18	-0.17	-0.04
Temporo-occipital cortex	-0.51**	-0.3	-0.49*	-0.33
Frontoparietal cortex	-0.42*	-0.24	-0.45*	-0.28
Superior parietal cortex	-0.38	-0.15	-0.28	-0.05
Occipital cortex	-0.35	-0.2	-0.37	-0.08

¹ Spearman's correlation coefficients, * $P < 0.05$; ** $P < 0.02$

The ratios between the weighted mean of rCMRGlc in the 3 frontal regions and the occipital region (0.86 ± 0.08 as against 0.95 ± 0.1), and between the weighted mean of rCMRGlc in the 3 frontal regions and the weighted mean of the 2 temporal regions (1.06 ± 0.06 vs 1.12 ± 0.07) were found to be significantly decreased in HD patients when calculations using the two-tailed Student's *t* test and Bonferroni's correction were carried out ($P < 0.05$). The ratio between the weighted mean of rCMRGlc in the 3 frontal regions and the weighted mean of rCMRGlc in the 2 parietal regions was not significantly different in HD patients compared with control subjects (1.02 ± 0.04 vs 1.05 ± 0.05).

The correlation coefficients between absolute values of rCMRGlc and the clinical data are shown in Tables 5 and 6. The severity of chorea showed a significant correlation only with the lentiform rCMRGlc ($P < 0.05$). The duration of chorea and the severity of dementia correlated significantly only with the rCMRGlc in the temporo-occipital and inferior parietal cortex. All other correlation coefficients for absolute values of rCMRGlc and the clinical data were not significant. This was especially true of the correlation coefficients between cerebellar rCMRGlc and the clinical status.

The correlation coefficients between the cortical ratios of striatal rCMRGlc are shown in Table 7. The cortical ratio of lentiform rCMRGlc correlated with the severity of chorea and with the degree of disability at a significance level of 0.05. There was no significant correlation between the cortical ratio of lentiform rCMRGlc and the severity

TABLE 7 CORRELATION OF CORTICAL RATIOS OF STRIATAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	<i>Duration of chorea</i>	<i>Severity of chorea</i>	<i>Severity of dementia</i>	<i>Degree of disability</i>
Caudate nucleus	0.04 ¹	-0.23	-0.28	-0.29
Lentiform nucleus	-0.22	-0.42*	-0.32	-0.44*

¹ Spearman's correlation coefficients, * $P < 0.05$

TABLE 8 CORRELATION OF CEREBELLAR RATIOS OF THALAMIC, STRIATAL, AND MEAN CORTICAL rCMRGlc WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	<i>Duration of chorea</i>	<i>Severity of chorea</i>	<i>Severity of dementia</i>	<i>Degree of disability</i>
Thalamus	-0.4 ¹	-0.35	-0.34	-0.51*
Caudate nucleus	-0.09	-0.25	-0.44*	-0.45*
Lentiform nucleus	-0.3	-0.39	-0.4	-0.49*
Mean cortex	-0.48*	-0.14	-0.58**	-0.55**

¹ Spearman's correlation coefficients; * $P < 0.05$; ** $P < 0.01$

TABLE 9. CORRELATION OF CEREBELLAR RATIOS OF rCMRGlc IN DIFFERENT CORTICAL REGIONS WITH THE SEVERITY OF SYMPTOMS IN PATIENTS WITH HUNTINGTON'S DISEASE (n = 23)

	<i>Duration of chorea</i>	<i>Severity of chorea</i>	<i>Severity of dementia</i>	<i>Degree of disability</i>
Inferior frontal cortex	-0.47* ¹	-0.27	-0.5*	-0.62**
Intermediate frontal cortex	-0.34	-0.05	-0.49*	-0.54**
Superior frontal cortex	-0.47*	-0.08	-0.5*	-0.4
Inferior temporal cortex	-0.5*	-0.28	-0.45*	-0.54**
Temporo-occipital cortex	-0.46*	-0.2	-0.59**	-0.66**
Frontoparietal cortex	-0.48*	-0.2	-0.61**	-0.62**
Superior parietal cortex	-0.47*	-0.11	-0.49*	-0.51*
Occipital cortex	-0.3	-0.19	-0.41	-0.4

¹ Spearman's correlation coefficients; * $P < 0.05$, ** $P < 0.01$.

of dementia or the duration of chorea. None of the correlation coefficients between the cortical ratio of caudate rCMRGlc and the severity of symptoms reached the significance level of 0.05.

The correlation coefficients between cerebellar ratios of rCMRGlc and the clinical data are shown in Tables 8 and 9. The duration of chorea correlated significantly with the CR of mean cortical rCMRGlc and with the CRs of rCMRGlc in all cortical regions except the intermediate frontal and occipital cortex. The severity of chorea did not correlate with the CR of any region studied, although the correlation coefficient for the CR of the lentiform nucleus ($r = -0.39$, $P < 0.07$) was almost significant. The severity of dementia correlated significantly with the CRs of the caudate rCMRGlc ($P < 0.05$), of mean cortical rCMRGlc ($P < 0.01$), and of rCMRGlc in all cortical

TABLE 10 CORRELATION OF THE SEVERITY OF CHOREA WITH STRIATAL GLUCOSE CONSUMPTION IN UNMEDICATED PATIENTS WITH HUNTINGTON'S DISEASE ($n = 12$)

	<i>Caudate</i> <i>rCMRGlc</i>	<i>Lentiform</i> <i>rCMRGlc</i>	<i>Cerebellar ratio</i> <i>of caudate</i> <i>rCMRGlc</i>	<i>Cerebellar ratio</i> <i>of lentiform</i> <i>rCMRGlc</i>	<i>Cortical ratio</i> <i>of caudate</i> <i>rCMRGlc</i>	<i>Cortical ratio</i> <i>of lentiform</i> <i>rCMRGlc</i>
Severity of chorea	-0.43 ¹	-0.36	-0.39	-0.3	-0.39	-0.32

¹ Spearman's correlation coefficients, all correlation coefficients not significant ($P > 0.05$).

regions studied except for the occipital rCMRGlc. The degree of disability correlated significantly with the CR of all cortical regions studied except the superior frontal and the occipital cortex.

The correlation coefficients for the severity of chorea and the absolute values of striatal rCMRGlc and its cerebellar and cortical ratios were of the same magnitude and not significant when the medicated patients were eliminated from the analysis (see Table 10).

DISCUSSION

In this study rCMRGlc was measured in a group of HD patients and normal subjects using the well-established standardized method introduced by Phelps *et al.* (1979) and Reivich *et al.* (1979). Various important limitations apply to this method and have been described elsewhere (for reviews, see Mazziotta and Phelps, 1986; Sokoloff, 1986). Several points of criticism concerning this method, however, need discussion. In this study arterialized venous blood was used in order to provide data for the plasma input curve into the brain. This method is widely used in PET studies because of its easy feasibility and noninvasiveness. Some criticism of its accuracy has been raised (Budinger *et al.*, 1985). This criticism, however, applies mainly to studies calculating rCMRGlc using FDG rate constants measured in the individual patient, and not to the procedure used in this study where standard rate constants were used. Moreover, a recent study by Tyler *et al.* (1988) has not reported significant differences between rCMRGlc values calculated using arterialized venous blood and those using arterial blood measured in two groups of normal volunteers.

An important limitation of measuring rCMRGlc in grey matter structures is a consequence of the partial volume effect leading to a mixture of grey matter, white matter, and cerebrospinal fluid (CSF) space in each ROI (Hoffman *et al.*, 1979). The partial volume effect influences rCMRGlc values measured in HD patients to a greater extent than those in normal subjects because HD patients have moderate cortical and severe striatal atrophy. This also applies to thalamic rCMRGlc, as thalamic atrophy occurs in some patients with HD (McCaughy, 1961); the ventrolateral thalamus may lose up to 50% of its microneurons (Dom *et al.*, 1976). In this study the partial volume effect is probably less important than in previous ones due to the improved spatial resolution of the PET scanner used (Mazziotta *et al.*, 1981). By using cross-sectional histograms as described by Young *et al.* (1986) to measure striatal rCMRGlc and by drawing the cortical and thalamic ROIs close to the peak values of these structures, additional efforts were made to minimize the partial volume effect. In HD patients,

the total cortical ROI area correlated negatively with the cortical atrophy evaluated on x-ray CT, implying that in patients with more severe cortical atrophy smaller cortical ROIs were drawn, presumably due to shrinkage of the brain in HD patients as described in neuropathological studies (e.g., Lange, 1981). Despite these efforts to minimize the partial volume effect, mean cortical rCMRGlc correlated significantly and negatively with the degree of cortical atrophy as determined on CT scan, indicating that in HD patients a decrease in rCMRGlc parallels the development of cortical atrophy to some extent.

The underestimation of rCMRGlc per mass unit of tissue due to the partial volume effect is a problem inherent in many PET studies comparing rCMRGlc in patients suffering from neurodegenerative diseases such as Alzheimer's disease (AD) with rCMRGlc measured in normal subjects. Controversial results have been reported in the literature. Some authors could clearly show that a correction of PET data for atrophy led to the expected increase of rCMRGlc in AD patients which was more pronounced in AD patients than in normal subjects because of the greater severity of brain atrophy in the AD group (Herscovitch *et al.*, 1986; Chawluk *et al.*, 1987). Preliminary data by Koeppe *et al.* (1989) indicate that—at least in AD patients—the observed decrease of cortical rCMRGlc cannot be ascribed to the influence of cortical atrophy alone. Decreases of rCMRGlc observed in patients with neurodegenerative diseases probably represent a combined effect of cell loss leading to atrophy, disturbed energy metabolism of single neurons, and functional inactivation due to malfunction of neurally interconnected brain regions leading to a loss of activating input. Even if a decrease in rCMRGlc were exclusively caused by inclusion of more white matter or CSF space into the region of grey matter due to atrophy and the partial volume effect, this would not affect the interpretation of a decrease of rCMRGlc as a malfunction of this region (caused predominantly by cell loss).

The principal finding of this study is that in HD patients cortical rCMRGlc is significantly reduced as compared with normal subjects in terms of absolute values. The group of HD patients was older by 1 yr than the group of normal subjects. Although the majority of studies have not found a significant decrease of rCMRGlc with age (e.g., Duara *et al.*, 1983; de Leon *et al.*, 1984, 1987), some authors state the contrary (Kuhl *et al.*, 1984b; Riege *et al.*, 1985; Yoshii *et al.*, 1988). The magnitude of these age-related changes, however, is not sufficient to explain a difference of approximately 17% in cortical rCMRGlc between two groups whose mean ages differ by only 1 yr.

The surface of the whole slice ROI placed on the PET slice corresponding to Talairach's slice 7–8 can be assumed to provide a relative measure of brain size (Hatazawa *et al.*, 1987a) and was smaller in HD patients than in normal subjects. The group of HD patients comprised more females than the group of normal subjects. These two conditions (smaller brain size, female sex) have been reported to be associated with higher rCMRGlc so that the decreased values found in HD patients are not due to different composition of both groups with regard to these conditions (Baxter *et al.*, 1987; Hatazawa *et al.*, 1987a,b; Yoshii *et al.*, 1988).

In this study, as in many others (e.g., Duara *et al.*, 1983; Goffinet *et al.*, 1989), a subjective ROI method was used. The cortical ROI sizes in HD patients, however, were smaller than those in normal subjects, and there was no negative correlation between the total cortical surface area analysed and mean cortical rCMRGlc. This indicates that

the difference in mean cortical rCMRGlc between both groups was not caused by erroneously drawing larger ROIs in the HD patients than in the normal subjects.

The data reported in this study suggest that cortical rCMRGlc is most markedly reduced in the frontal cortex and thus confirm the significant decrease of an anterior/posterior ratio as reported by Kuhl *et al.* (1982). This study, however, is the first to report a significant decrease of cortical rCMRGlc in terms of absolute values in a large group of HD patients. The decrease of cortical rCMRGlc was approximately 17%, and thus not as marked as the decrease observed for the striatum. This could possibly explain the failure of previous authors (Kuhl *et al.*, 1982, 1984a; Young *et al.*, 1986; Berent *et al.*, 1988) to detect this difference since the PET scanners used in those studies had a lower resolution than the high-resolution PET PC-4096 used in this study (11 to 16 mm vs 4.8 mm); the partial volume effect which increases with decreased spatial resolution (Mazziotta *et al.*, 1981) might have masked this difference.

Another possible explanation of discrepant results reported in previous studies are differences in patient selection: as mean cortical rCMRGlc normalized to the cerebellum correlates negatively with the duration of chorea (*see* Table 8), studies enrolling patients at an early stage of the disease (Young *et al.*, 1986; Berent *et al.*, 1988) will not detect a decrease of cortical rCMRGlc in HD patients.

The finding of decreased rCMRGlc in the cortex is in good agreement with previous neuropathological studies demonstrating cortical cell loss and consecutive brain atrophy in this group of patients (Alzheimer, 1911; McCaughey, 1961; Lange, 1981). The presence of advanced cortical cell loss in patients with HD was further confirmed by studies with x-ray CT revealing the presence of cortical atrophy in these patients (Sax *et al.*, 1983; Terrence *et al.*, 1977; Oepen and Ostertag, 1981). In view of this evidence and the presence of moderate cortical atrophy diagnosed by CT in the HD patients studied, the decrease of cortical rCMRGlc is probably mainly related to direct cortical pathology and not to functional inactivation. As the cortex and the striatum are, however, jointly involved in at least two neuronal circuits (the principal striatal circuit and the fourth 'accessory' striatal circuit according to Nieuwenhuys *et al.*, 1988), a contribution of functional inactivation to the observed decrease of cortical rCMRGlc cannot be excluded completely. Moreover, Laplane *et al.* (1989) have recently described the occurrence of relative prefrontal hypometabolism in patients with lesions involving the lentiform nuclei, which they ascribed to a process of deafferentation of the prefrontal cortex. This lends support to the hypothesis that the observed decrease of the frontal rCMRGlc is at least partly caused by functional inactivation and thus offers a potential explanation for the significant hypofrontality of rCMRGlc observed in HD patients in this study and in that by Kuhl *et al.* (1982).

Since in previous studies no reduction of cortical rCMRGlc was found (Kuhl *et al.*, 1982), recent observations correlating rCMRGlc with clinical symptoms in HD patients (Young *et al.*, 1986; Berent *et al.*, 1988) have been performed exclusively for striatal rCMRGlc. As there is high interindividual variation of rCMRGlc in HD patients as well as in normal subjects, these authors have used indices of striatal metabolism normalized to maximal cortical rCMRGlc for this purpose. The use of these reference values, however, precludes the detection of possible relationships between cortical rCMRGlc and clinical symptoms. Since the cerebellar rCMRGlc seemed least affected in this group of HD patients, and since cerebellar rCMRGlc correlates significantly

with rCMRGlc in other brain regions in normal individuals, it seems appropriate to consider cerebellar rCMRGlc an 'internal standard' in patients with HD and to use cerebellar rCMRGlc as a reference value in this patient group. In addition to these normalized values this study reports on correlations between absolute values of rCMRGlc and the severity of symptoms in HD as well as between cortical ratios of striatal rCMRGlc and the clinical data. To our surprise, there was only a poor correlation between the degree of chorea as assessed by a clinical rating scale with both absolute rCMRGlc, the cortical ratio of rCMRGlc, and the cerebellar ratio (CR) of rCMRGlc in the striatum. This seems to be in contradiction to a study published by Young *et al.* (1986), demonstrating that rCMRGlc of the putamen normalized to the peak cortical activity correlated highly significantly with chorea in a group of 15 early to midstage HD patients. As the group of patients studied herein also included severely disabled patients, this discrepancy most likely is a result of differences concerning the severity of the disease in the two groups of patients studied. Chorea, which means hyperkinesia, is known to increase continuously to a peak in the midstage period of HD and to decrease from thereon as the patient sometimes even develops rigidity in later stages (Shoulson, 1981; Folstein *et al.*, 1986). Although neuroleptic treatment may suppress hyperkinesia (Adams and Victor, 1985) and thus might interfere with the validity of the correlation coefficients reported here between striatal metabolism and the degree of chorea, there was no major change of these correlation coefficients when the medicated patients were eliminated from the analysis (*see* Table 10). It therefore appears unlikely that in this group of patients the absence of a strong correlation between striatal metabolism and the degree of chorea is due to the inclusion of medicated patients.

Several authors have attributed the dementia of HD patients directly to pathology of the basal ganglia (McHugh and Folstein, 1975; Cummings and Benson, 1984). This concept was introduced approximately a decade ago (McHugh and Folstein, 1975) leading to the classification of the dementia encountered in HD patients as subcortical. The PET studies by Kuhl *et al.* (1982, 1984a) and Berent *et al.* (1988) reporting on normal cortical rCMRGlc in HD patients and on highly significant correlations between striatal rCMRGlc (normalized to cortical rCMRGlc) and psychometric test results in a group of early to midstage HD patients have lent considerable support to this concept. There are, however, only sparse clinical data to corroborate this concept (Whitehouse, 1986). In a CT study, Sax *et al.* (1983) found a positive and significant correlation between CT measures of caudate atrophy and cognitive function in a group of HD patients with both mild and severe impairment. In these patients cortical atrophy, however, was also present, and was reported to be worse in those patients with more severe impairment.

The data reported herein show that—in addition to a poor correlation of the degree of dementia with the CR for caudate rCMRGlc—the degree of dementia correlated best with the CR of mean cortical rCMRGlc in this group of HD patients. Even 2 correlation coefficients between absolute values of rCMRGlc in the frontoparietal and temporo-occipital cortex attained significance. In view of this observation the hypothesis that dementia in manifest HD is directly linked to subcortical pathology (Cummings and Benson, 1984) needs be reconsidered.

In the group of patients with HD studied here, the correlation coefficients between PET data and the severity of dementia were highest not in the frontal cortex, which seems the cortical region most severely affected in HD, but in the more posterior parts

of the brain (frontoparietal and temporo-occipital cortex). This may partly be due to the composition of the battery of psychometric tests used, since only the SKT includes frontal lobe oriented tasks. Nevertheless, the above-presented correlation coefficients between the PET data and the cognitive impairment of the HD patients show that the dementia encountered in this group of HD patients shares some common features with the dementia encountered in patients with Alzheimer's disease (AD). In AD patients, specific patterns of reduced rCMRGlc have been reported, with a reduction of rCMRGlc or rCMRO₂ in the parieto-occipital cortex prevailing also at an early stage of this disease (Frackowiak *et al.*, 1981; Foster *et al.*, 1983; de Leon *et al.*, 1983) and correlating with dementia (Chase *et al.*, 1987).

Many efforts have been made to assess the disability of HD in the performance of everyday tasks. The scale used in this study is a modification of the widely accepted Shoulson-Fahn scale and is supposed to measure the overall functional capacity of a patient with HD, thus encompassing deficits of many neuronal pathways. It is therefore not surprising to find that the CRs for most brain regions studied correlate significantly with the degree of disability.

Summarizing the above, it can be concluded that in patients with manifest HD, in addition to the more pronounced decrease of striatal rCMRGlc, a reduction of cortical rCMRGlc is also present, and that this reduction contributes to the severity of the clinical findings. As the reduction of cortical rCMRGlc correlated significantly with the degree of dementia, a modification of the concept of 'subcortical dementia' in HD patients seems to be indicated.

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VESTIBULAR FUNCTION IN PERIODIC ALTERNATING NYSTAGMUS

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SUMMARY

The vestibulo-ocular reflex of 4 patients with periodic alternating nystagmus (PAN) was studied in detail. Rotational testing was used to investigate the horizontal semicircular canal-ocular reflex, canal-otolith interaction, and the dynamic otolith-ocular reflex. Results indicated abnormal gain and phase of the horizontal semicircular canal-ocular reflex during sinusoidal rotation and a variable rate of decay of postrotatory responses. Each patient had abnormal canal-otolith interaction. An enlarged modulation component of the dynamic otolith-ocular response was observed in each patient. This study supports the idea that PAN is caused by an instability in the velocity storage element, a hypothetical neural circuit that perseverates the eye movement response to both vestibular and optokinetic stimulation. Further, we postulate that PAN may be caused by lesions of the cerebellar uvula and nodulus or their connections with the brainstem vestibular nuclei.

INTRODUCTION

Periodic alternating nystagmus (PAN) is a rare eye movement abnormality characterized by a horizontal jerk nystagmus whose slow component velocity changes in amplitude and direction periodically (Jung and Kornhuber, 1964). The periodicity of this nystagmus is often about 4 min with 2 min of right beating and 2 min of left beating nystagmus. PAN may be congenital or acquired. The acquired condition has been associated with various disease states including spinocerebellar degeneration (Gorman and Brock, 1950; Plant, 1982), multiple sclerosis (Jung and Kornhuber, 1964; Keane, 1974; Larmande 1982), Arnold-Chiari malformation (Towle, cited in Davis and Smith, 1971; Baloh *et al.*, 1976; Meienberg and Hoyt, 1980; Leigh *et al.*, 1981), posterior fossa neoplasm (Karp and Rorke, 1975), cryptococcosis (Halmagyi *et al.*, 1980; Leigh *et al.*, 1981), arachnoid cyst of the posterior fossa (Towle and Romanul, 1970), and neurosyphilis (Susac and Henry, 1975). Although 5 cases have been studied neuropathologically (Towle and Romanul, 1970; Karp and Rorke, 1975; Keane, 1974; Susac and Henry, 1975; Towle, cited in Davis and Smith, 1971), the specific localization and pathophysiology of PAN are not known.

We have had the opportunity to study the vestibular function of 4 patients with PAN. Testing was designed to investigate the horizontal semicircular canal-ocular reflex, canal-otolith interaction, and the dynamic otolith-ocular reflex. Our aim was to gain insight into the neurological localization and pathophysiology of PAN.

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CASE REPORTS

Case 1

A 51-yr-old woman presented with a 10-yr history of gait instability. Her symptoms had increased in severity during the 3 yrs before evaluation. For 12 months before evaluation she had had difficulty in reading. Past medical history was also significant for paroxysmal coughing spells, difficulty in swallowing, and frequent hiccupping. Cranial nerve examination revealed PAN and a diminished gag reflex without other abnormality. Motor examination showed normal strength with hyperactive reflexes in all extremities. Plantar responses were flexor bilaterally. Coordination testing was normal. Sensory examination revealed diminished vibration and position sense in both feet. Gait was ataxic.

A magnetic resonance (MR) scan (fig. 1A) showed a type I Arnold-Chiari malformation with the cerebellar tonsils extending to the upper border of the C2 laminae. The patient was taking no medication. She underwent suboccipital craniectomy and C1, C2 laminectomy. On opening the dura, dysplastic-looking tonsils were noted at the level of the C2 laminae and appeared to be tightly constricted at the foramen magnum and upper cervical canal. The uvula was similarly constricted just below the rim of the foramen magnum (fig. 1B). A fourth ventriculo-subarachnoid shunt was inserted and a wide decompressive duraplasty performed with lyophilized cadaver dura. Postoperatively the patient was much improved symptomatically. Neurological examination revealed that PAN was present only with loss of visual fixation. The gag reflex was brisk. There was improvement in vibration and position sense in both feet. Gait was improved. There was no complaint of difficulty swallowing or of hiccupping.

Case 2

A 25-yr-old woman with a past history of postvaricella encephalitis at the age of 9 yrs and significant residual impairment of cognitive and motor function was evaluated for difficulty with vision and balance. Cranial nerve examination revealed a visual acuity of 20/80 in the right and 20/200 in the left eye. Visual fields were full. There was an exotropia of more than 60 prism dioptres and a left hypertropia of 10 prism dioptres. PAN was observed. Motor examination showed normal strength. The tendon reflexes and sensation were normal. She had an intention tremor on finger-to-nose testing and her gait was ataxic.

An MR scan (fig. 1C) revealed prominent enlargement of the fourth ventricle and marked atrophy of the cerebellar vermis. Medication at the time of initial eye movement testing was clonazepam 2 mg per day. The patient was subsequently treated with baclofen 30 mg per day, which provided symptomatic relief of imbalance, although her PAN persisted. Rotational testing was performed while she was taking both clonazepam and baclofen.

Case 3

A 34-yr-old man presented with a complaint of lightheadedness and gait instability since age 15 yrs. His symptoms were slowly progressive. There was no other significant past medical history. Family history was negative. He used no medications. Cranial nerve examination revealed PAN but was otherwise normal. Motor examination showed normal strength. The tendon reflexes were normal but the plantar responses were extensor bilaterally. Sensation was normal. There was dysmetria during finger-to-nose and heel-knee-shin testing and his gait was ataxic. An MR scan (fig. 1D) revealed marked cerebellar atrophy. The patient was treated with baclofen, 30 mg per day which provided minimal symptomatic relief of imbalance; PAN persisted. Rotational testing was performed while the patient was taking baclofen.

Case 4

A 44-yr-old man presented with a long-standing complaint of blurred vision and difficulty focusing. He indicated that abnormal eye movements had been present since birth. His only other complaint was that of a low amplitude head tremor that was exacerbated by anxiety. He had no complaint of imbalance or incoordination. There was no other significant past medical history. Family history was negative. He used no medications. Cranial nerve examination revealed PAN but was otherwise normal. There was minimal head titubation. Muscle strength and tendon reflexes were normal, as were coordination, sensation and gait. An MRI scan was normal. The patient declined treatment with baclofen.

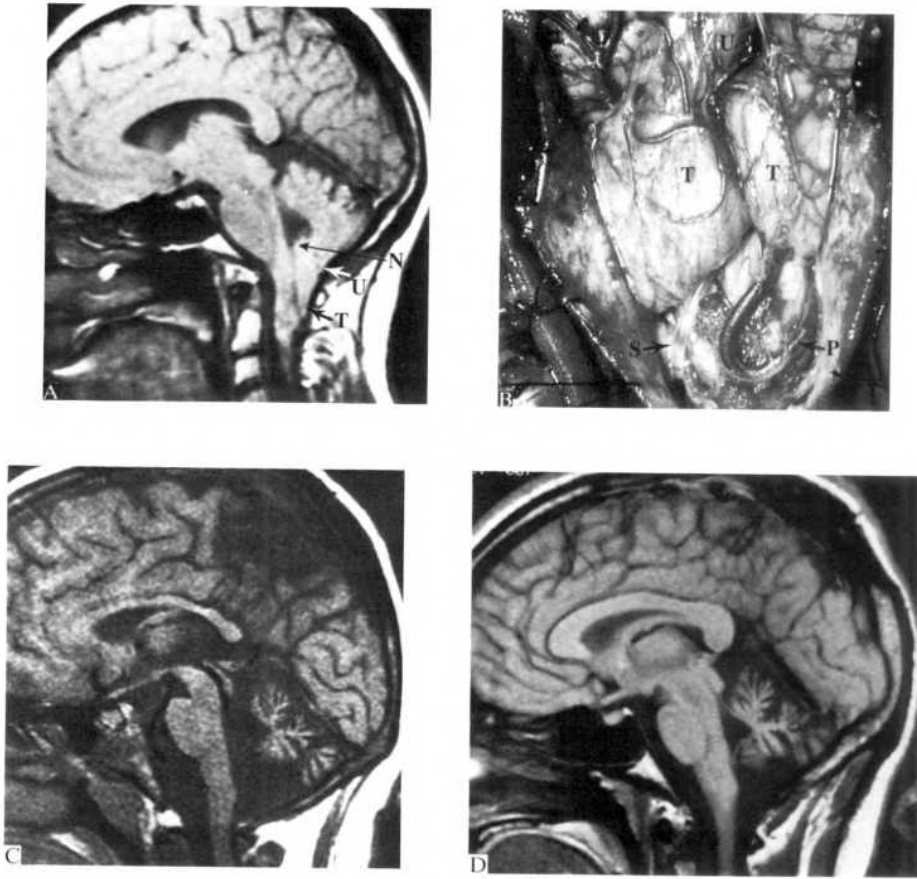


FIG. 1. A, *Case 1*. Sagittal MR scan showing Arnold-Chiari type I malformation. The triangular peg of cerebellar tonsil (T) extends down to the upper border of the C2 laminae. The uvula (U) is lying below the rim of the foramen magnum, and the nodulus (N) is at the rim. All three structures appear compressed at the craniovertebral junction. B, *Case 1*. Intraoperative photograph showing the low-lying dysplastic tonsils (T), the descended loop of the right posterior inferior cerebellar artery (P) below the right tonsil, and the silastic fourth ventriculo-subarachnoid shunt (S) below the left tonsil. The uvula (U) is just below the rim of the foramen magnum. C, *Case 2*. Midsagittal MR scan showing marked atrophy of the cerebellar vermis and ex-vacuo enlargement of the fourth ventricle and cisterna magna. D, *Case 3*. Midsagittal MR scan showing atrophy of the cerebellar hemispheres and vermis.

METHODS

All testing was performed following receipt of each patient's informed consent.

Spontaneous nystagmus

Eye movements were recorded by electro-oculography (EOG) using silver-silver chloride electrodes attached bitemporally to record horizontal eye position. Electrodes were placed above and below one eye for recording vertical eye position and blink artefact. The EOG signal was fed to a d.c.-coupled signal amplifier with a high frequency cut-off of 40 Hz. The amplified filtered eye movements were recorded on a chart recorder for computation of slow component eye velocity (SCV). Spontaneous nystagmus in each of the patients was recorded for at least one complete cycle of their PAN at the start of each test session. The effect of visual fixation was determined by first recording the patients' nystagmus with eyes

open behind dark goggles and then by recording their nystagmus while they attempted to fixate a small visual target. The effect of changes in static head position on each patient's PAN was assessed by recording spontaneous nystagmus in the supine, head right, head left, right lateral, and left lateral positions. In addition, the effect of brief 30° horizontal gaze deviation was recorded.

Ocular motor testing

Using EOG, each patient underwent testing of horizontal voluntary saccades and pursuit tracking. The amplified filtered EOG signal was analysed by a digital computer to determine saccadic velocity, accuracy and latency. Saccades were tested by instructing the subjects to fixate a laser-generated target that moved horizontally at random intervals in time and space. Pursuit tracking was tested with a laser target moving sinusoidally at a frequency of 0.2 Hz and $\pm 22.6 \text{ deg} \cdot \text{s}^{-1}$.

Earth vertical axis rotational testing—sinusoids

The horizontal semicircular canal-ocular reflex was studied with earth vertical axis (EVA) rotational testing using a conventional (vertical axis) rotatory chair affixed to a 38 Nm turntable. Rotation was in the yaw plane, and consisted of both single frequency sinusoids and velocity trapezoids. Yaw refers to angular motion about an axis that is oriented upright with respect to the body, i.e., motion about the rostral-caudal body axis. Single frequency sinusoids included rotations at 0.0025, 0.005 and 0.01 Hz with peak velocities of between 110 and 150 $\text{deg} \cdot \text{s}^{-1}$ and at 0.05 Hz with a peak velocity of between 85 and 105 $\text{deg} \cdot \text{s}^{-1}$. During rotation, patients wore dark goggles to prevent visual fixation.

Eye position was measured with EOG, amplified, filtered, and recorded on a chart recorder. Additionally, eye position and rotational chair velocity were recorded on a Tandberg 100 FM tape recorder for off-line analysis. To determine SCV versus time, the data recorded on FM tape were fed to a PDP 11/73 computer for analog to digital conversion. The eye position data were then analysed by a nystagmus algorithm (Wall and Black, 1981) that yielded SCV versus time data.

For 0.0025, 0.01 and 0.05 Hz stimulation, a definite rotational response was evident in all patients based upon a change in the frequency of the periodicity of their nystagmus from that of their spontaneous PAN to that of the rotational stimulus (see fig. 3A, B, D). For 0.005 Hz stimulation, when the stimulus frequency and the patients' PAN frequency were nearly identical, a definite rotational response was evidenced by a shift in phase from that of their spontaneous PAN to about 90° phase lead with respect to the rotational stimulus. To demonstrate optimally that the patients' nystagmus during the 0.005 Hz rotation was indeed a result of the vestibular stimulation, the rotational stimulus was begun so that the relative phase of the patients' PAN with respect to the rotational stimulus would initially be 90° of phase lag (see fig. 3C).

The SCV responses were used to compute gain and phase of the horizontal vestibulo-ocular reflex (VOR). To accomplish this, each patient's SCV response was used to compute the parameters A, ϕ_{res} , B, ϕ_{pan} , and C of the equation:

$$\text{SCV}(t) = A \cdot \sin(2\pi f_{\text{res}} \cdot t + \phi_{\text{res}}) + B \cdot \sin(2\pi f_{\text{pan}} \cdot t + \phi_{\text{pan}}) + C \quad (1)$$

where f_{res} was set equal to the rotational stimulus frequency and f_{pan} to the patient's PAN frequency, A represents the amplitude of the patient's response at the stimulus frequency, ϕ_{res} the phase of the patient's response at the stimulus frequency, B, the amplitude of the patient's underlying PAN while undergoing sinusoidal rotation, ϕ_{pan} the phase of the patient's underlying PAN during sinusoidal rotation, and C, a constant bias term. Because the patients' PAN represented a subharmonic for 0.01 Hz and 0.05 Hz stimulation, and because of the small number of cycles taken at 0.0025 Hz, we elected to estimate the parameters A, B, C, ϕ_{res} and ϕ_{pan} of equation (1) using a least squares algorithm. Gain of the VOR at each frequency was computed as the ratio: A/stimulus amplitude. Phases of the VOR were referenced to the inverse of the stimulus velocity (Olson *et al.*, 1981).

For 0.005 Hz data, each patient's SCV response was used to compute the parameters A, ϕ_{res} , and C of the equation:

$$\text{SCV}(t) = A \cdot \sin(2\pi \cdot 0.005 \cdot t + \phi_{\text{res}}) + C \quad (2)$$

where A represents the amplitude of the patient's response, ϕ_{res} the phase of the patient's response, and

C a constant bias term. A least squares fit was performed to estimate the parameters of equation (2). Gain and phase were computed as above.

Earth vertical axis rotational testing—trapezoids

To evaluate further the horizontal semicircular canal-ocular reflex, and to provide a baseline for canal-otolith interaction testing, velocity trapezoids were performed using 45 s of yaw rotational acceleration at $2 \text{ deg} \cdot \text{s}^{-2}$ followed by rotation at a constant velocity of $90 \text{ deg} \cdot \text{s}^{-1}$ clockwise, i.e., to the right, until the patients' perrotatory vestibular nystagmus was negligible and they exhibited their baseline PAN. The patients were then decelerated at $100 \text{ deg} \cdot \text{s}^{-2}$ until the rotation chair stopped. So that the effect of head tilt on postrotatory responses (see below) could be assessed accurately, we chose four clearly identifiable stimulus onset (deceleration) times: (1) just after the patient's PAN changed from right beating to left beating; (2) at the peak of left beating nystagmus; (3) just after the patient's PAN changed from left beating to right beating nystagmus; and (4) at the peak of right beating nystagmus.

For velocity trapezoid testing, eye movements were recorded with EOG and analysed to yield SCV versus time. In order to estimate the first-order time constant of the decay of postrotatory nystagmus, we computed the slope of a straight line fit through the natural logarithm of the SCV versus time using a least squares algorithm. The time constant represents the time required for the response to fall to 37% of its initial value. This method provides only a first approximation to the postrotatory vestibular response in that the time course of the patients' postrotatory SCV was more complicated than that expected from a single time constant system. Because of this complicated postrotatory response, we computed the dominant time constant using the first 5, 10 and 20 s of the postrotatory SCV data. These time constant estimates (and the unprocessed EOG data) served as a baseline against which to assess the effect of changes in static head position on postrotatory responses.

Effect of static head tilt on postrotatory nystagmus

Semicircular canal-otolith interaction was studied by assessing the effect of static head tilt on postrotatory nystagmus using the EVA yaw rotational trapezoid protocol described above except that immediately following the cessation of rotation, the patients were passively tilted 45° forwards at the waist while assuring no neck flexion or extension. The stimulus was, therefore, a brief EVA rotational deceleration with subsequent head tilt, which is known to shorten the time course of EVA postrotatory nystagmus in normal subjects (Benson, 1966). To optimize the likelihood of observing this expected response, the patients were decelerated (and then immediately tilted) following prolonged constant velocity clockwise rotation at each of the four stimulus onset times noted above. (Postrotatory head tilt data were available for Case 1 only at the onset of left beating nystagmus.) The SCV following deceleration with head tilt was compared visually with the SCV obtained following an identical deceleration without head tilt. Also, the dominant time constant of the postrotatory responses with head tilt was estimated in a manner identical to that used for the postrotatory responses without head tilt.

Off-vertical axis rotational testing

Each of the 4 patients underwent dynamic otolith-ocular testing using yaw rotation about an axis that was tilted either 30° off-vertical (Cases 2, 3, 4), or 90° off-vertical (Case 1). Rotation consisted of $60 \text{ deg} \cdot \text{s}^{-1}$ velocity trapezoids that commenced with the patient positioned in the nose-up position in the rotational device. For each test, rotation was counterclockwise, i.e., from nose-up to left lateral to nose-down to right lateral to nose-up for at least 60 s.

The eye movement response to off-vertical axis rotation was recorded with eyes open behind dark goggles using EOG in the same manner as for EVA testing. The amplified, filtered eye position signal was fed to both a chart recorder and to a PDP 11/04 computer for analog to digital conversion or to an FM tape recorder for subsequent analog to digital conversion by a PDP 11/73 computer. The eye position data were analysed off-line using a nystagmus algorithm (Wall and Black, 1981) that yielded SCV versus time data. These SCV data were evaluated qualitatively to determine the presence of a modulation component, a periodic waxing and waning of the SCV whose periodicity is that of the change in orientation of the subject with respect to gravity (Benson and Bodin, 1966), i.e., $1/6 \text{ Hz}$ for a $60 \text{ deg} \cdot \text{s}^{-1}$ constant velocity rotation.

RESULTS

Spontaneous eye movements and ocular motor function

All 4 patients presented with PAN both with and without visual fixation. However, postoperatively, Case 1 had PAN only in the dark. Each patient's PAN was a purely horizontal jerk nystagmus whose SCV waxed and waned in a pattern that was not entirely sinusoidal (fig. 2). PAN cycle lengths were 210, 220, 213 and 220 s for Cases 1, 2, 3, and 4, respectively. In none of our 4 patients was there any observable effect of change in static head position in terms of either PAN pattern or cycle length.

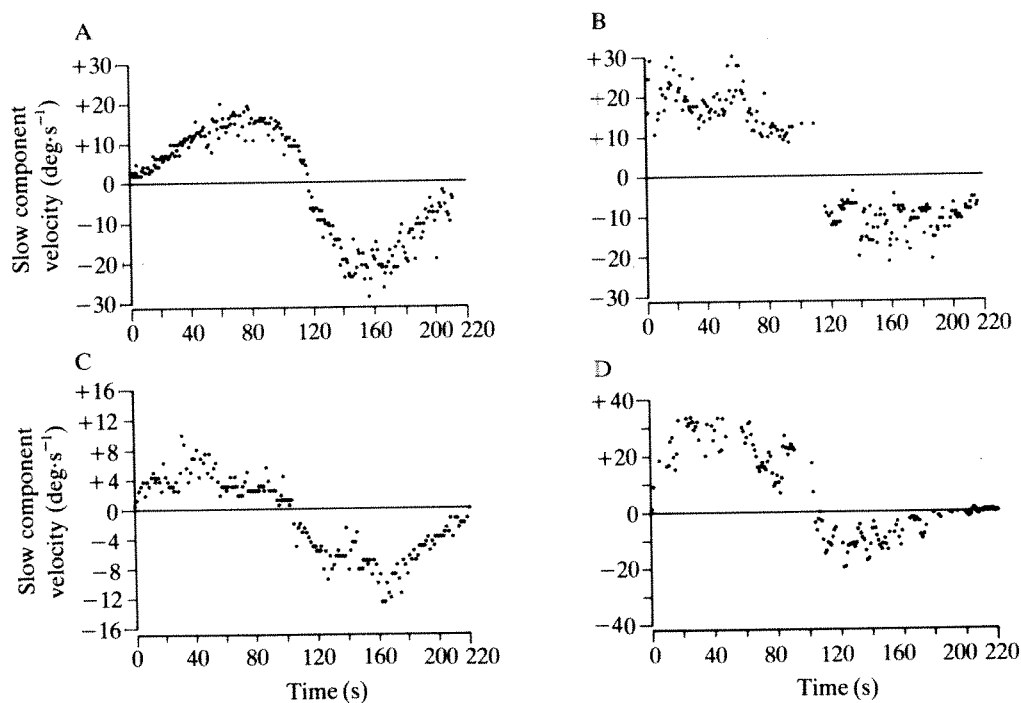


FIG. 2. Slow component velocity versus time for each of 4 patients with periodic alternating nystagmus. A, Case 1; B, Case 2; C, Case 3; D, Case 4.

Each of our 4 patients had normal saccadic velocity, latency and accuracy with no hypometria or hypermetria. Horizontal pursuit tracking was symmetrically impaired in all 4 patients. Of interest, however, is that pursuit tracking in Case 1 was markedly improved postoperatively.

Earth vertical axis sinusoids

During sinusoidal EVA rotation, the patients exhibited unequivocal semicircular canal-ocular responses as evidenced by a change in the periodicity of the alternation of nystagmus direction during rotation at 0.05, 0.01 and 0.0025 Hz (*see* fig. 3A, B, D), and by a change in the timing of the alternation of nystagmus direction during rotation

at 0.005 Hz (*see* fig. 3C). That is, the patients' nystagmus alternated in direction at the frequency of rotational vestibular stimulation at 0.05, 0.01 and 0.0025 Hz; for 0.005 Hz, when the vestibular stimulus was at nearly the same frequency as the patients' spontaneous PAN, the phase, i.e., timing relationship, between the stimulus and response reached about 90° phase lead after about one period (200 s) regardless of when in the patients' PAN cycle the stimulus was begun. In addition to this well defined vestibular response at the rotational stimulus frequency, we noted a superimposition of the patients' ongoing PAN and their rotational responses (except at 0.005 Hz). By estimating the peak SCV at both the stimulus frequency and the patient's PAN frequency (except at 0.005 Hz when these frequencies were nearly equal), the relative magnitude of the vestibular response and the patients' ongoing PAN was estimated (*see* Methods). As indicated in the Table, at 0.05 Hz and to a lesser extent at 0.01 and 0.0025 Hz, there was evidence that each patients' baseline PAN persisted to some extent during rotational responses. This superimposition of vestibular response and baseline PAN is clearly seen in fig. 3A and B. For all but 1 trial (0.0025 Hz, Case 2), the magnitude of the vestibular

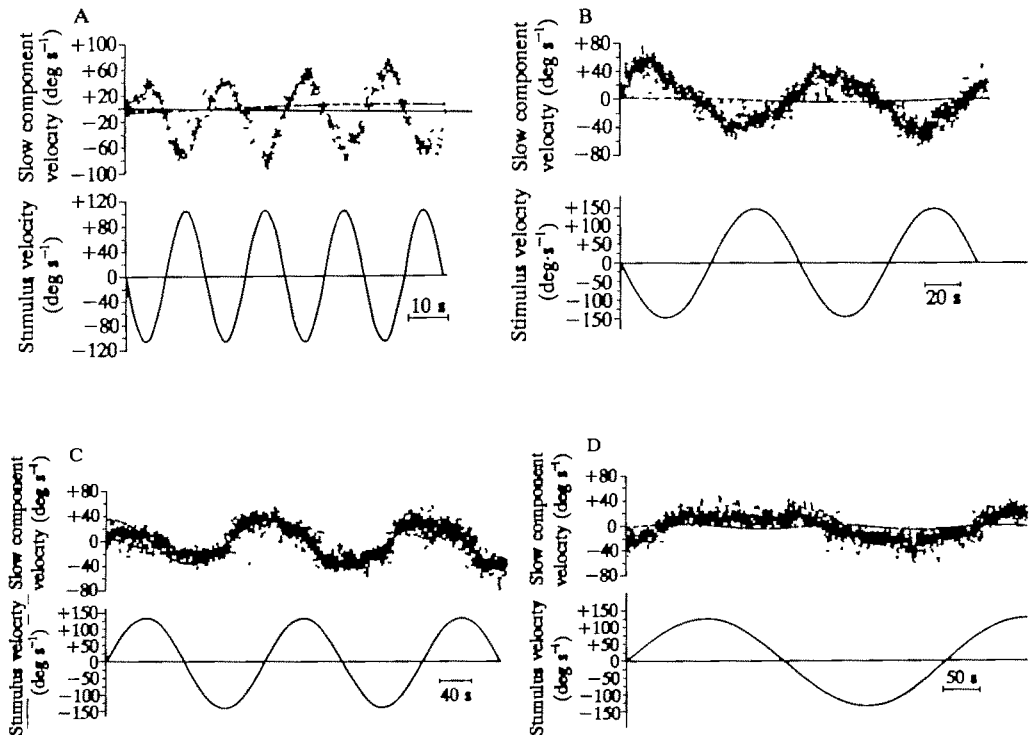


FIG. 3. Slow component velocity response to sinusoidal rotation at four different frequencies in a patient with periodic alternating nystagmus (Case 3). A, 0.05 Hz; B, 0.01 Hz; C, 0.005 Hz; D, 0.0025 Hz. Note that the patient's slow component velocity alternates direction at the rotational stimulus frequency in each trace. For A, B and D the dashed line indicates the change in slow component velocity at the frequency of the patient's PAN. For C, the solid line represents the least squares fit at 0.005 Hz using only the data after the first 200 s of rotation. The dashed line in C represents the projection backwards in time of the least squares fit of the eventual rotational response so that the phase shift induced by the rotational stimulus can be clearly discerned.

TABLE SINUSOIDAL ROTATIONAL RESPONSES IN PATIENTS WITH PERIODIC ALTERNATING NYSTAGMUS

<i>Magnitude of vestibular response (deg·s⁻¹)</i>					
<i>Case</i>	<i>0.0025 Hz</i>	<i>0.005 Hz</i>	<i>0.01 Hz</i>	<i>0.05 Hz</i>	
1	26.3	43.9	51.2	38.8	
2	14.8	36.7	50.3	87.0	
3	25.3	38.5	38.0	53.5	
4	43.0	58.3	77.8	75.5	
<i>Magnitude of underlying PAN (deg·s⁻¹)</i>					
<i>Case</i>	<i>At rest</i>	<i>0.0025 Hz</i>	<i>0.005 Hz</i>	<i>0.01 Hz</i>	<i>0.05 Hz</i>
1	17.9	0.8	—	1.8	12.6
2	18.1	49.0	—	9.0	19.7
3	7.1	4.6	—	3.0	12.5
4	18.3	9.2	—	3.9	11.3
<i>Ratio of magnitude of underlying PAN during rotation to magnitude of PAN at rest</i>					
<i>Case</i>	<i>0.0025 Hz</i>	<i>0.005 Hz</i>	<i>0.01 Hz</i>	<i>0.05 Hz</i>	
1	0.05	—	0.10	0.70	
2	2.71	—	0.50	1.10	
3	0.65	—	0.42	1.76	
4	0.50	—	0.21	0.62	

response far exceeded the magnitude of the underlying PAN during rotation. The Table also indicates that, except for 3 trials, the magnitude of each patients' underlying PAN during rotation was smaller than the magnitude of their PAN at rest.

Fig. 4 shows the patients' gain and phase data at each rotational frequency with comparison data from a group of normal subjects. As in normal subjects, the gain of the horizontal VOR of the patients with PAN increases with increasing frequency. However, in general, the patients' gain was greater than normal. The phase of the patients' horizontal VOR shows a surprising result in that their phase lead at 0.05 Hz was less than the average for normals (in 3 of 4 cases), while at 0.0025 Hz, each patient's phase lead was much greater than normal. This pattern of abnormality has not been reported previously for any vestibular disorder. Phase leads at 0.0025 Hz have not been reported previously for any human subjects.

Earth vertical axis trapezoids

Following brief rotational EVA deceleration from clockwise rotation at $90 \text{ deg}\cdot\text{s}^{-1}$, regardless of the time in the PAN cycle at which the stimulus was delivered, each patient had a definite postrotatory response with nystagmus in the expected direction (i.e., left beating) whose peak SCV ranged from 60 to $90 \text{ deg}\cdot\text{s}^{-1}$ and was thus clearly differentiated from their baseline PAN. Following a variable time interval after rotational deceleration, each patients' PAN resumed, although its time course had been altered. The SCV decayed with a dominant time constant that depended on the amount of data used (*see Methods*). If only the first 5 s of postrotatory response data were used, the

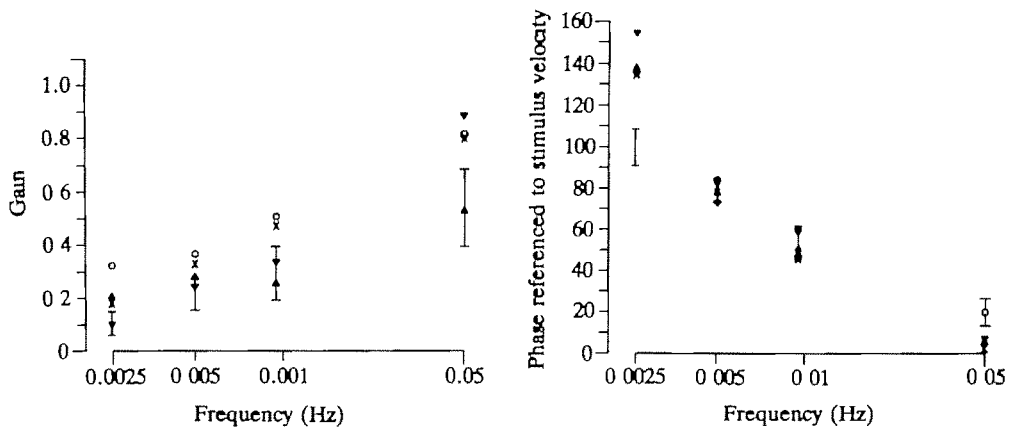


FIG. 4. Gain and phase of the horizontal VOR as a function of frequency for 4 patients with periodic alternating nystagmus. X = Case 1, ∇ = Case 2, $\triangle$ = Case 3, $\circ$ = Case 4. For comparison, the bars are the responses (mean $\pm$ 1 SD) of an age-matched group ($n = 6$) of normals.

dominant time constant had an average value of 11.9 ± 6.9 s as compared with 6.3 ± 2.8 s found in normals. If 10 or 20 s of postrotatory data were used, the dominant time constant had an average value of 20.2 ± 10.9 s as compared with 12.1 ± 4.6 s found in normals. This dependence of the time constant estimate on the amount of postrotatory data used suggests that a single time constant descriptor of the horizontal semicircular canal-ocular reflex is an oversimplification and may reflect a nonlinearity in the VOR such that VOR dynamics depend on the magnitude of the SCV. That our patients' time constants exceeded normal is unusual in that vestibular system disease often results in a shortened dominant time constant (Baloh *et al.*, 1984; Furman and Becker, 1989).

Effect of static head tilt on postrotatory nystagmus

For each of our 4 patients, there was no apparent difference between EVA postrotatory responses with and without 45° of head tilt. This result was evident qualitatively by scrutinizing the data and was confirmed quantitatively by comparing the dominant time constants of the postrotatory responses with and without head tilt. This lack of effect of head tilt was found regardless of the time in the PAN cycle at which the vestibular stimulus was delivered and is shown for 1 of our patients in Fig. 5B. This finding contrasts markedly with the well-known effect of head tilt on EVA postrotatory responses of normal subjects (Benson, 1966), i.e., a definite foreshortening of postrotatory nystagmus (*see* fig. 5A) and suggests that our patients had abnormal semicircular canal-otolith interaction.

Off-vertical axis rotational testing

Fig. 6 shows the SCV versus time of Case 3 in response to a counterclockwise rotation at a constant velocity of $60 \text{ deg} \cdot \text{s}^{-1}$ while tilted 30° off-vertical. Rotation was begun when the patient's PAN cycle changed from right beating to left beating. It can be seen that the off-vertical axis rotational response contains a periodic modulation of the SCV

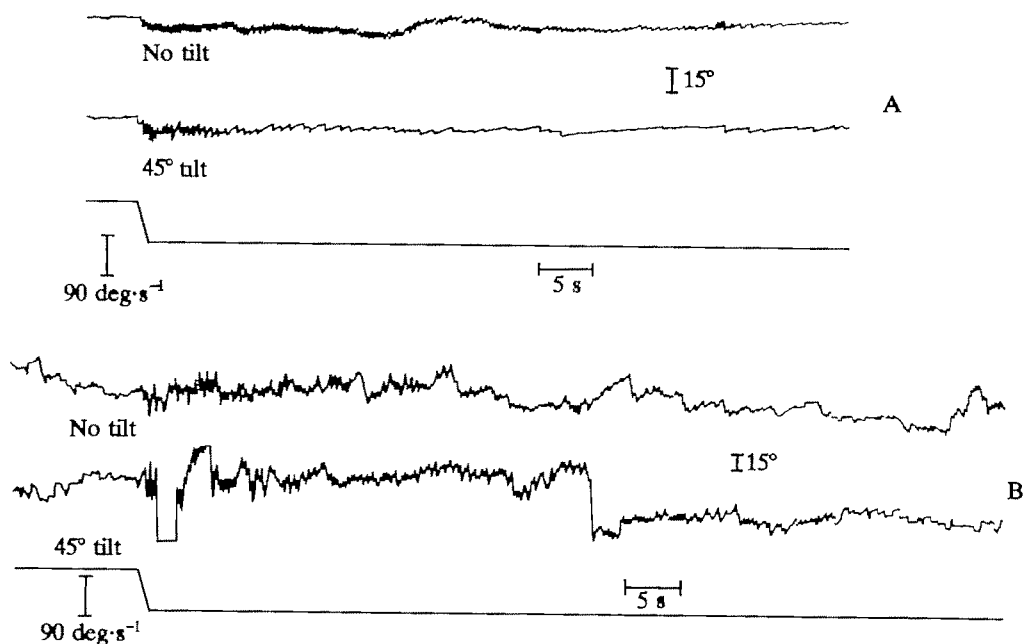


FIG. 5 Effects of head tilt on postrotatory vestibular responses. A, responses from a normal subject. B, responses from *Case 1*. Note that whereas the postrotatory nystagmus of the normal subject is markedly diminished by head tilt, the response of the patient is not altered by head tilt.

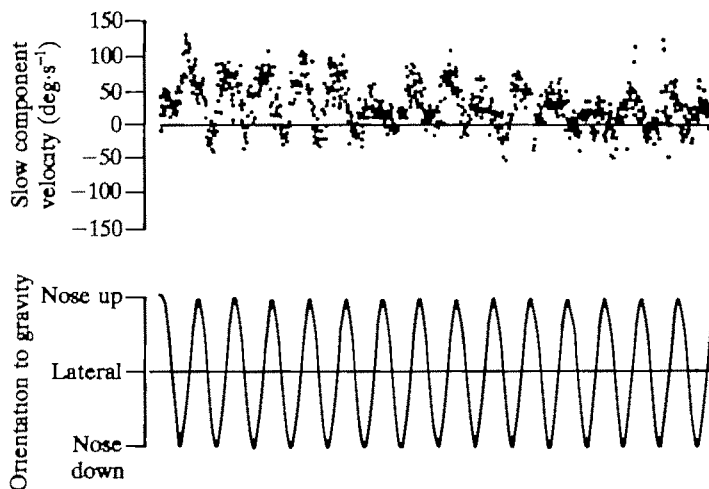


FIG. 6 Slow component velocity of nystagmus induced by off-vertical axis rotation in a patient with periodic alternating nystagmus (*Case 2*). Note the presence of a modulation component, i.e., periodic waxing and waning of slow component velocity at a frequency equal to that of the periodic change in orientation with respect to gravity.

whose frequency is that of the periodic change in the patient's orientation with respect to gravity (0.16 Hz) and whose magnitude is about $50 \text{ deg} \cdot \text{s}^{-1}$. Thus the SCV response to off-vertical axis rotation contains a modulation component whose peak-to-peak magnitude exceeds that of normal subjects, which is about $12 \text{ deg} \cdot \text{s}^{-1}$ (Darlot *et al.*, 1988). Responses of the other 3 patients also showed unequivocal modulation components of large magnitude suggesting a high amplitude dynamic otolith-ocular response.

DISCUSSION

Vestibular function has been studied previously in only a few cases of PAN (Toglia, 1968; Baloh *et al.*, 1976; Leigh *et al.*, 1981). These studies, which have been limited to the horizontal semicircular canal-ocular reflex, have revealed (1) increased gain of the horizontal VOR (Baloh *et al.*, 1976; Leigh *et al.*, 1981); (2) clearly discernible superimposition of rotational responses and the patients' ongoing PAN (Toglia, 1968; Baloh *et al.*, 1976); and (3) a rapid decay of postrotatory responses (Leigh *et al.*, 1981). Our data do not agree entirely with these studies and indicate that: (1) horizontal VOR gain, although increased on average, may be normal in some patients with PAN at certain rotational frequencies; (2) although VOR responses are clearly superimposed on patients' PAN at some sinusoidal frequencies (e.g., 0.05 and 0.01 Hz), rotational responses at frequencies nearly equal to that of a patient's PAN may obscure their ongoing PAN; (3) the decay of postrotatory responses of patients with PAN is not more rapid than normal. In addition to those refinements, our data extend the findings from previous studies of vestibular responses in patients with PAN (Toglia, 1968; Baloh *et al.*, 1976; Leigh *et al.*, 1981) and indicate that these patients have: (1) phase leads for the horizontal semicircular canal-ocular reflex that are less than normal at higher frequencies (e.g., 0.05 Hz) and greater than normal at very low frequencies (e.g., 0.0025 Hz); (2) abnormal canal-otolith interaction, as evidenced by a lack of foreshortened postrotatory nystagmus following head tilt; and (3) the presence of an enlarged modulation component during dynamic otolith-ocular testing.

The pathophysiology of PAN is not known. However, it has been hypothesized by several investigators that PAN relates to a hyperresponsiveness of the VOR (Jung and Kornhuber, 1964; Baloh *et al.*, 1976; Leigh *et al.*, 1981). Leigh *et al.* (1981) proposed that PAN is caused by a relative instability in the so-called velocity storage element, a hypothetical neural circuit that perseverates the eye movement response to both vestibular and optokinetic stimulation. Leigh *et al.* developed a mathematical model in which the velocity storage element consisted of both a negative and a positive feedback loop with PAN being caused by an excessive efficacy (gain) of the positive feedback loop, resulting in oscillatory behaviour. That is, they modelled the central vestibulo-optokinetic system of patients with PAN as a nonlinear second-order system with a very small damping ratio that depended on eye velocity. We stimulated the Leigh *et al.* (1981) model using a digital computer package that emulates an analog computer (TUTSIM, Applied i, Palo Alto, California) and tested its response to earth vertical axis rotational sinusoids and trapezoids. We determined that the formulation of Leigh *et al.* is consistent with our patients' vestibular responses in that (1) the estimates of the VOR time constants were comparable for the model and the patients (9.7 s vs 11.9 s, respectively, using the first 5 s of postrotatory data and 13.0 s vs 12.1 s using 10 or

20 s of postrotatory data), and (2) phase leads were diminished as compared with normal at frequencies above 0.005 Hz and increased as compared with normal at frequencies below 0.005 Hz for both the model responses and the patient responses. Our patients' phase data are characteristic of second-order systems with small damping ratios (Kamen, 1987) with a natural frequency of about 0.005 Hz, nearly that of our patients' PAN.

Our patients' PAN can be considered to represent the activity of a biological oscillator (Pavlidis, 1973). This notion is strengthened by the frequency-dependent masking and superimposition of PAN by rotational vestibular responses. At high rotational frequencies, both the PAN and the vestibular response were present, but at frequencies near that of the patients' PAN, the ongoing PAN component was less prominent. This frequency-dependent masking is consistent with a property of biological oscillators known as entrainment (Pavlidis, 1973), wherein an external periodic input causes the self-oscillatory component to vanish. The frequency range of the entrainment effect usually depends upon the characteristics of the oscillator and on the amplitude and frequency of the external stimulus. We determined that the PAN model postulated by Leigh *et al.* (1981) exhibited entrainment at all the test frequencies used in this study. This differs from our patients' responses where entrainment was seen only at a limited number of frequencies. Our simulation of the Leigh *et al.* (1981) model also revealed an amplitude dependence of the entrainment phenomenon that depended on the specific characteristics of the central vestibular nonlinearity. These simulation studies suggest that our understanding of PAN could be refined by examining the entrainment phenomenon of patients with PAN in more detail, possibly using sinusoids of various amplitudes as well as various frequencies.

Also consistent with the hypothesis that PAN is caused by a relatively unstable velocity storage element is that baclofen is known to be of benefit for some patients with acquired PAN (Halmagyi *et al.*, 1980; Leigh *et al.*, 1981; Larmande, 1982; Plant, 1982). Although the specific mode of action of baclofen in PAN is not known, its beneficial effects can be understood in light of recent findings by Cohen *et al.* (1987) who showed that baclofen shortens the time course of postrotatory VOR responses in monkeys by decreasing the effectiveness of the velocity storage element. Thus baclofen may be of benefit in PAN because it reduces the neural activity in an inappropriately disinhibited velocity storage element, thereby resulting in a reduction of relatively unstable behaviour. The 2 patients in our study who were prescribed baclofen gained minimal symptomatic relief without a change in their PAN.

Most of the previously reported cases of PAN have revealed little effect of visual fixation on the ongoing nystagmus. However, several cases have been reported in which PAN was present only with loss of visual fixation induced in the laboratory by recording with eyes closed (Toglia, 1968) or with a loss of visual fixation following binocular visual system lesions (Davis and Smith, 1971; Cross *et al.*, 1982). All our patients presented with PAN both with and without visual fixation, although 1 patient (Case 2) may have had impaired fixational abilities secondary to poor visual acuity. Of interest is that 1 of the patients (Case 1), following a neurosurgical procedure, had PAN only in the dark. Studies in monkey have indicated that the cerebellar flocculus is of particular importance for the suppression of vestibular nystagmus by visual fixation (Miles and Fuller, 1975; Lisberger and Fuchs, 1978; Zee *et al.*, 1981; Waespe *et al.*, 1983), suggesting that our patient may have had a partial return of cerebellar floccular function postoperatively. Support of this idea is the observation that rhesus monkeys with

experimentally induced lesions of the uvula and nodulus that spare the flocculus have PAN only in the dark (Waespe *et al.*, 1985). That the flocculus plays a role in fixation suppression of PAN may explain why some patients, when evaluated at the bedside, are noted to have only brief periods of nystagmus separated by quiet epochs. Their nystagmus may be manifested only when the velocity of their underlying PAN exceeds their floccular-dependent fixational abilities.

The neurological localization of PAN is not known. However, information from various sources enables us to formulate a hypothesis in this regard: (1) all 5 cases of PAN that have been studied neuropathologically had lesions in the caudal midline cerebellum and/or in the vicinity of the vestibular nuclei in the medulla (Towle and Romanul, 1970; Towle, cited in Davis and Smith, 1971; Keane, 1974; Karp and Rorke, 1975; Susac and Henry, 1975); (2) recent data from the rhesus monkey indicate that selective lesions of the cerebellar uvula and nodulus can induce PAN (Waespe *et al.*, 1985); (3) our patients with PAN showed no effect of head tilt on postrotatory nystagmus, an abnormality that has been localized to the cerebellar uvula and nodulus (Waespe *et al.*, 1985; Hain *et al.*, 1988). We hypothesize, therefore, that PAN in humans may be caused by lesions of the cerebellar uvula and nodulus or their connections with the brainstem vestibular nuclei. Consistent with this localization is that patients with PAN have been shown to have ocular motor abnormalities characteristic of cerebellar lesions (Baloh *et al.*, 1976; Halmagyi *et al.*, 1980; Meienberg and Hoyt, 1980) and some patients with PAN have an associated downbeat nystagmus (Keane, 1974). Based on the interrelationship between PAN and visual fixation discussed above, although lesions of the cerebellar uvula and nodulus or their connections with the brainstem vestibular nuclei may underlie PAN, lesions of the cerebellar flocculus appear to be critical only for the manifestation of PAN during visual fixation.

Our data indicate that the off-vertical axis rotational response of patients with PAN contains a modulation component (Benson and Bodin, 1966) that is larger than normal. This increase in the magnitude of dynamic otolith-ocular responses is analogous to the increase in semicircular canal-ocular reflex gain seen in our patients and previously reported in patients with vestibulocerebellar lesions (Zee *et al.*, 1974; Baloh *et al.*, 1981). The neural pathways that underlie the modulation component are unknown. However, a recent mathematical model of the nystagmus induced by off-vertical axis rotation assumes that the modulation component is derived from the periodic waxing and waning of neural activity in eighth nerve otolithic afferents with subsequent processing by the central nervous system (Hain, 1986). Thus, in addition to the importance of the cerebellar uvula and nodulus and their connections with the brainstem vestibular nuclei for stability in the velocity storage element (Waespe *et al.*, 1985) and for normal canal-otolith interaction (Waespe *et al.*, 1985; Hain *et al.*, 1988), our data suggest that these structures may also be important for determining the magnitude of the modulation component of dynamic otolith-ocular reflexes.

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THE ANATOMICAL BASIS OF THE CAECOCENTRAL SCOTOMA

NEW OBSERVATIONS AND A REVIEW

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SUMMARY

It is shown that the 'papillomacular bundle' of optic nerve fibres, although a concept discussed frequently in the clinical literature, lacks a clear anatomical definition. It is suggested that the explanation for this is that the 'bundle' was originally described in autopsy studies of toxic amblyopia, not normal anatomy. The optic nerve fibre projection and vascular architecture of the caecocentral region of the retina is described. These anatomical features are discussed in relation to a number of possible anatomical explanations for the fact that a caecocentral scotoma is the characteristic field defect found in toxic amblyopia. We have been unable to identify a distinct anatomical feature which might explain this vulnerability but suggest that the problem has not as yet been clearly addressed by anatomists.

INTRODUCTION

The caecocentral scotoma was first described in 'tobacco-alcohol' or 'toxic' amblyopia in the last century (*see, e.g.,* Förster, 1877). Examples of the field defect have been published many times (*e.g.,* Carroll, 1935) and a figure from the textbook of Traquair (1947) is reproduced as fig. 1 as an illustration. It has been shown that in the very much rarer examples of visual failure due to vitamin B₁₂ deficiency a similar field defect occurs (Turner, 1940; Benham, 1951). A caecocentral scotoma may be found in a variety of other conditions (such as optic neuritis, Leber's optic neuropathy and 'tropical' and 'Jamaican' amblyopia) and central rather than caecocentral scotomas have been reported in otherwise typical examples of toxic amblyopia (*e.g.,* Kupersmith *et al.*, 1983), but most authorities agree that a caecocentral scotoma is the characteristic field defect in toxic amblyopia. The explanation for the vulnerability of the projection of the retinal region subserving this part of the visual field in toxic amblyopia is unknown. In this paper we emphasize some of the uncertainties concerning the anatomical features of this projection and discuss the problem in the context of the recent literature and some original observations.

TERMINOLOGY

A central concept in much of the clinical literature on toxic amblyopia is the 'papillomacular bundle' of optic nerve fibres. The view often expressed is that the central retinal projection has distinct features which give rise to a greater vulnerability in certain disease processes. It is important to appreciate, however,

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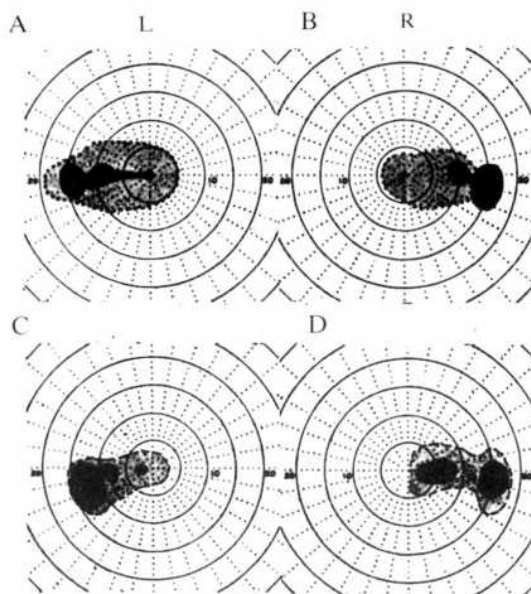


FIG. 1. Typical examples of caecocentral scotomas: reproduced from Traquair (1947).

that the 'papillomacular bundle' was not described in studies of normal human or primate anatomy. Uhthoff, having previously discussed the visual field findings in toxic amblyopia (1880), published an autopsy study (Uhthoff, 1886) in which he named the degenerated optic nerve fibres as the papillomacular bundle 'papillomakuläre Opticusfaser'. Uhthoff quotes Bunge (1884) as having used this term in exactly the same context previously, whereas other autopsy reports had referred to the macular bundle ('maculäre Faser') (Samelsohn, 1882; Vossius, 1882). In all these cases it was shown that the characteristic clinical abnormality—bilateral relative scotomata to coloured targets extending in an oval from the fovea to the blind spot—was associated with degeneration of optic nerve fibres occupying the temporal side of the optic nerve just behind the eye. These fibres were found to have taken up a position in the centre of the nerve towards the chiasm. Fig. 2 shows Uhthoff's sketch of the arrangement as he observed it in one such case (Uhthoff, 1886). It was on the basis of this pathological material that the concept of the 'papillomacular bundle' arose as is clearly stated in the textbook of Wilbrand and Saenger (1904) who provided the following definition. 'The papillomacular bundle (papillomakuläre Bündel) encircles all the fibres supplying the macula and supplies at the same time the retinal area which is represented in the visual field as a horizontal oval situated between the blind spot and the focal point. . . . The papillomacular bundle contains both crossed as well as uncrossed fibres.' Subsequently, involvement of the same group of optic nerve fibres has been demonstrated in primates reared in captivity on an entirely vegetarian diet (Scherer, 1937; van Bogaert, 1962; Hind, 1970, 1972) as a result of vitamin B₁₂ deficiency, confirming that in nonhuman primates the same fibre group may show a similar susceptibility.

The appreciation of the fact that the 'papillomacular bundle' was described in such clinical cases is of importance for a number of reasons. First, it is clear that this group is composed of the axons of retinal ganglion cells of both the nasal and temporal hemifoveae plus the retinal area between the optic disc and the fovea: as we shall see, different authorities have not agreed on the anatomical definition of the 'papillomacular bundle'. Secondly, there is at times a circularity in the arguments concerning the vulnerability of the 'papillomacular bundle' in toxic amblyopia: for example Jestico *et al.* (1984) stated that the 'papillomacular bundle' is particularly susceptible to the effect of toxins and that its involvement in tobacco amblyopia is therefore evidence for the toxic nature of the disorder.

Although in his earlier book Polyak considered the 'papillomacular bundle' to consist only of the projection of the nasal hemifovea (Polyak, 1941), it is clear that subsequently he considered it to be synonymous with the foveal projection stating that (Polyak, 1957, p. 297): ' . . . there is a rather wide intermediate temporal sector, in the left eye corresponding to between 2 and 4 o'clock . . . where the numerous thin

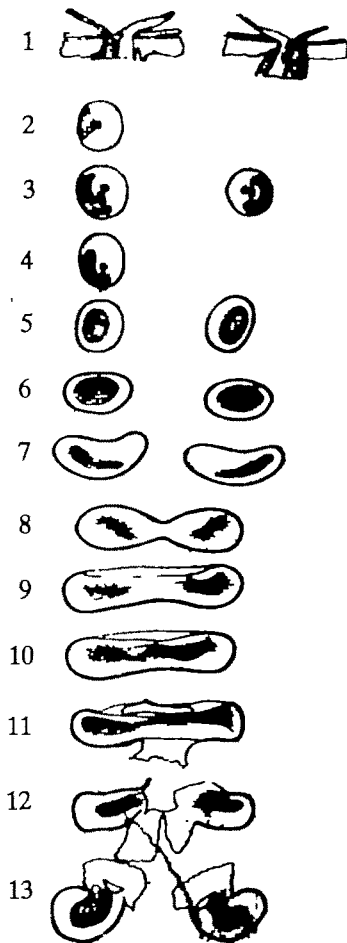


FIG. 2. The course of the 'papillomacular bundle', as described by Uthoff (1886) in an autopsy study of a case of tobacco-alcohol amblyopia.

bundles from the central area and fovea reach the papilla: the "papillomacular bundle". It is also clear that Polyak had reservations concerning the use of the term—which appears in his book always in quotation marks—and later in the same volume (p. 336) he refers to the 'foveal or so-called papillomacular bundle'.

The confusion surrounding the terminology led Benham (1951), in discussing the development of caecocentral scotoma in vitamin B₁₂ deficiency, to state that 'The papillomacular bundle innervates the foveal area of the retina, and damage to the bundle might be expected to produce a symmetrical scotoma of 5° radius . . .'. Hence he found it impossible to ascribe the caecocentral scotoma to damage to the papillomacular bundle as he understood it. Still others have assumed (*see, e.g.,* Posner and Schlossman, 1948) that the axons of the ganglion cells between the fovea and the optic disc project to the nasal side of the disc and are not included in the 'papillomacular bundle'. This suggestion was not refuted until 1963 (Hoyt and Tudor, 1963).

More recently Glaser has stated (1978) that 'The ganglion cells subserving the central cone system send axons directly to the temporal aspect of the optic disc, forming the papillomacular bundle'. In a study of the nerve fibre diameter spectra of the primate retina, Ogden (1984) defined as papillomacular only those fibres originating within 0.5 mm of the fovea. Ogden studied individual 'bundles' in the nerve fibre layer (*see* Discussion) and highlighted a further difficulty with the term 'papillomacular bundle, because the foveal projection is composed of many such groups of fibres and Ogden was compelled to describe

a number of 'papillomacular bundles' as making up the foveal projection. Clearly this is a substantial deviation from the original usage of the term and its importance to caecocentral scotoma.

We propose that the term 'papillomacular bundle' should be abandoned for the following reasons. (1) Both in the nerve fibre layer and in the optic nerve (as discussed further below) there is no discrete bundle; rather the ganglion cell axons are grouped into a number of bundles or fascicles. (2) The term has also been used to describe the foveal projection. This is a departure from its original meaning and has left us without an adequate description of the anatomical basis of the caecocentral scotoma.

In recent years the details of the anatomy of the inner retinal layers have been studied by a number of workers. It is our objective to discuss the evidence that is relevant to the retinal morphology and optic nerve projection subserving the caecocentral retina, an issue which, in part because of the confused terminology discussed above, has not been addressed directly. Throughout this discussion we will employ the term 'foveal projection' (FP) to define the fibres arising from the central 5° of the visual field and the term 'caecocentral projection' (CCP) to describe the projection of the fovea plus the parafoveal nasal retina which together constitute the projection related to the caecocentral scotoma illustrated in fig. 1. In the light of this distinction we are concerned particularly with a comparison of nasal and temporal parafoveal retina, rather than a comparison of central and peripheral retina.

RESULTS

Experiment 1: The anatomical features of the caecocentral projection

The purpose of the first experiment is to demonstrate the cell bodies and the intraretinal trajectories of the axons of the ganglion cells which contribute to the foveal projection (FP) and the caecocentral projection (CCP) as defined above.

Methods

The experiments were performed on *Macaca mulatta* and the procedures have previously been described in detail (Perry *et al.*, 1984). Briefly, a pellet of the axoplasmically transported enzyme horseradish peroxidase (HRP) was deposited in one optic nerve of a monkey under sodium thiopentone anaesthesia. The deposit of HRP was made in the nerve a few mm behind the globe. After a period of 24 or 48 h the animal was given a lethal dose of sodium pentobarbitone and intracardiac perfusion performed. After exsanguination with 0.9% saline the eyes were removed, the retina was dissected free and fixed flat on a glass slide. The HRP was revealed by a modified Hanker-Yates histochemical protocol. The sensitive histochemical method visualizes the axon, cell body and dendritic tree of a substantial number of ganglion cells. More than 20 preparations were studied, 4 were found to illustrate the fibre architecture of the projection of caecocentral retina and the results of these are illustrated below.

Results

Fig. 3 shows an example of an HRP placement which has labelled fibres which enter the optic disc on its temporal side. It can be clearly seen that the ganglion cells labelled are those in the foveal region. The margin of the fovea is defined histologically (following Polyak) as the point at which the ganglion cell layer is thickest—around 1000 μm eccentricity. Those ganglion cells which lie in the retinal region between the fovea and the optic disc are also labelled. This projection, therefore, is from the retinal region which corresponds to the caecocentral scotoma and hence demonstrates the organization of the fibres which constitute the caecocentral projection (CCP). It should be noted that the extent of labelling of ganglion cell bodies on the temporal side of the fovea is small.

Two points are important for the discussion which follows. First, that the foveal projection does run together with the fibres originating in this region of nasal extrafoveal retina and must continue to do so for at least 3–4 mm behind the eye where the pellet of HRP has been placed. Secondly, the suggestion that the CCP consists only of fibres

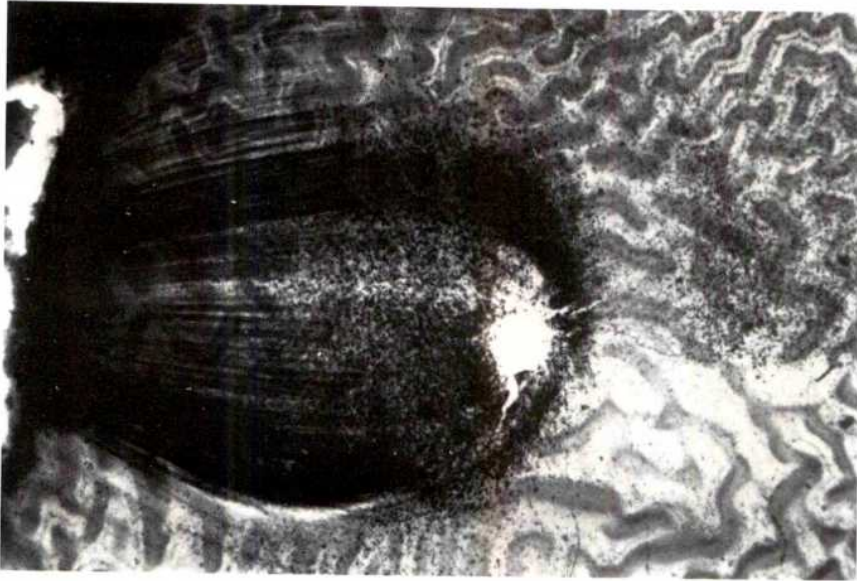


FIG. 3. Photomicrographs of flat-mounted *M. mulatta* retina. The fovea is in the centre of the preparation and the optic disc at the left border; the distance separating the fovea and optic disc is approximately 3.0 mm. In this preparation a substantial proportion of the retinal ganglion cells and their axons projecting to the medial side of the optic disc are shown following HRP injection into the optic nerve just behind the eye. The group of optic nerve fibres labelled constitute the projection of the caecocentral region of the retina and hence corresponds to the 'papillomacular bundle' as defined by Uhthoff and others.

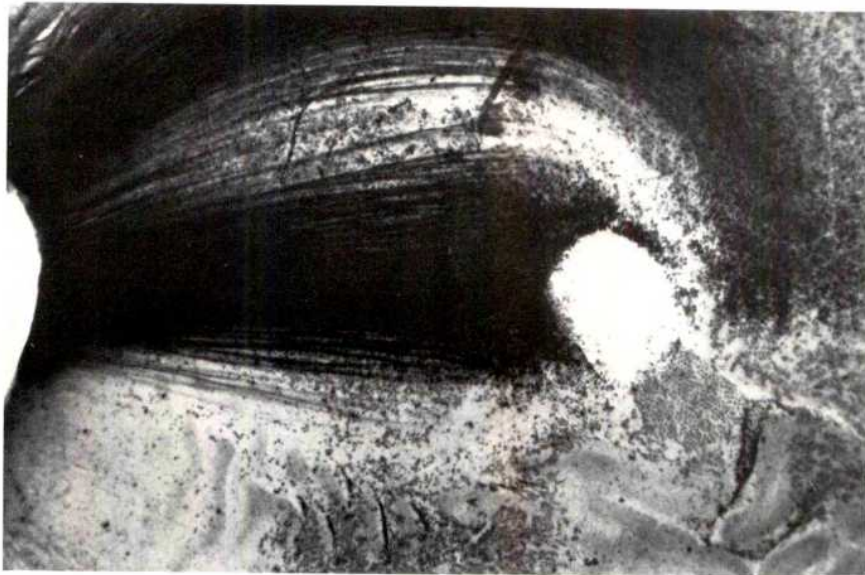


FIG. 4. Flat-mounted retinal preparation as described for fig. 3. The projection of the nasal hemifovea is shown, together with a superior arcuate bundle.



FIG. 5. Flat-mounted retinal preparation as described for fig. 3. The projection of the superior temporal quadrant of the fovea is shown. Note that the nerve fibres project within the arcuate bundles.

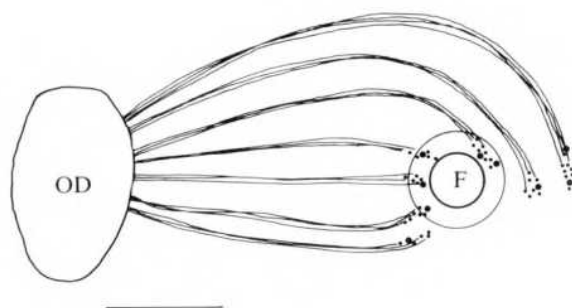


FIG. 6. Individual retinal ganglion cells and their axons have been traced, using a drawing tube from a further preparation similar to those shown in figs 3, 4 and 5. The course taken by the optic nerve fibres to the temporal side of the optic disc is clearly shown. Note that there is no anatomical feature which can be used to distinguish the foveal projection from the arcuate bundles to which ganglion cells in the temporal hemiretina project. Instead, all axons tend to avoid the horizontal meridian and there is a gradual transition from axons projecting directly to the optic nerve head to those projecting in an curvilinear or arcuate manner. The scale provided represents 1 mm. OD = optic disc; F = fovea.

which pursue a direct course to the disc is clearly an oversimplification. Instead, there is a continuum in the architecture of the fibres, from those originating in the nasal hemifovea which pursue a rectilinear course, through those projecting from the temporal hemifovea which are curvilinear, to the arcuate bundles originating in the temporal extrafoveal retina.

This arrangement is further emphasized in the examples shown in fig. 4, where the ganglion cells and axons of the nasal hemifovea have been selectively stained and fig. 5

where, together with the superior arcuate fibres, the bundles arising in the superior temporal quadrant of the fovea have been stained. It can be seen that the curvilinear course of these fibres differs in degree only from the arrangement of the arcuate fibres which enter the disc at its superior temporal margin. It is not possible on the basis of the fibre arrangement alone, without a knowledge of the origin of the fibres, to define the limits of the foveal projection (FP) or the CCP and we can see clearly why the concept of the 'papillomacular bundle', arising as it did from the autopsy material, has defied a clear definition based on normal anatomy. The course taken by the foveal fibres is shown schematically in fig. 6. All the fibres have been drawn from a single preparation.

Experiment 2: Regional variations in retinal vasculature

The purpose of this experiment was to investigate the possibility that regional variations in the capillary density of the ganglion cell layer of the retina may account for the susceptibility of the retina projection subserving the caecocentral region of the visual field. The vascular pattern of the macaque retina is generally held to be very similar to that found in humans (*see, e.g., Shimizu and Ujiié, 1978*).

Methods

Eyes were obtained from *M. mulatta* and *M. fascicularis* which had been perfused by the intracardiac route with 10% formol-saline at the end of experiments unconnected with the visual system. The retina was rapidly removed and flattened on a glass slide. Fixation was continued with 4% paraformaldehyde in 0.1 M sodium cacodylate for a further 2 h. The retina was then washed in the same buffer for 2 h. The retinal vasculature was revealed by the presence of nucleotide diphosphatase activity following the method of Novikoff and Goldfischer (1961). Thiamine pyrophosphate (Sigma) or adenosine diphosphate (Sigma) were used as the substrates, the latter giving the best results. The retinæ were incubated at 37° C for up to 2 h. Following the histochemistry the retinæ were attached to a gelatinized slide and dehydrated. Shrinkage was minimal and confined to the far peripheral retina. The retinæ were examined as whole mounts. Two eyes were examined from each species, the findings were consistent and the results from a single sample are illustrated below (fig. 7).

To assess the density of the capillaries in the central retina the following procedure was used. The blood vessels in the optic fibre layer or the ganglion cell layer were drawn at a magnification of $\times 400$ with the aid of a drawing tube. The area sampled was $0.285\ \mu\text{m} \times 0.285\ \mu\text{m}$ at intervals of 1.0 mm. The length of the capillaries was then measured using a bitpad and microprocessor (RML, Oxford).

Results

It is not our intention to describe the vascular pattern of the primate retina in full since this has been previously well documented. We examined quantitatively whether the density of capillaries in the optic fibre and ganglion cell layer around the fovea varied in a way that might shed light on the pathogenesis of the caecocentral scotoma.

The results obtained at 6 retinal locations are shown in fig. 7. The values for the ganglion cell layer itself—the superficial capillary net, and the nerve fibre layer—the radial peripapillary net (these terms are described more fully in the Discussion) are given separately. As the nerve fibre layer becomes thicker closer to the optic disc increasing numbers of capillaries within this layer are found. The capillary density in the ganglion cell layer itself, however, does not differ significantly at a given distance from the fovea whether at a nasal, temporal or inferior location. These locations were chosen because those situated between the fovea and the disc which lie within the CCP are vulnerable in toxic amblyopia, those temporal and inferior to the fovea are not.

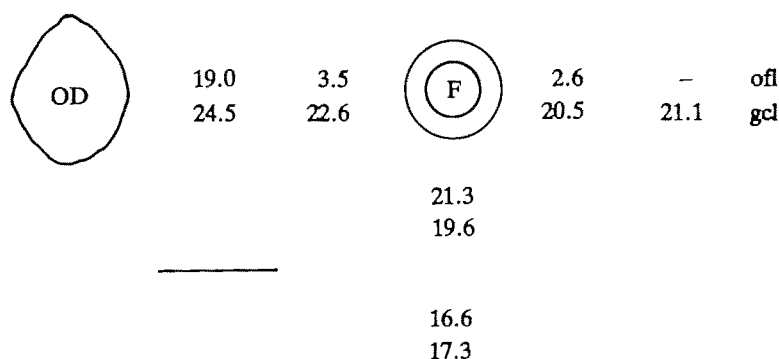


FIG. 7. The capillary density within the optic fibre layer (off) and the ganglion cell layer (gcl) has been measured at 6 locations around the fovea (F). The numbers indicate the total capillary length in μm contained within an area measuring $0.285 \mu\text{m} \times 0.285 \mu\text{m}$. Capillary density within the off is greater where the off itself is thicker, density within the gcl remains relatively constant and certainly does not differ significantly in the 2 areas sampled nasal to the fovea (which are vulnerable in toxic amblyopia) and the other 4 areas (which are not vulnerable). Scale 1 mm. OD = optic disc.

DISCUSSION

This discussion is concerned with the implications of aspects of retinal anatomy to the caecocentral type of scotoma in toxic amblyopia and related conditions. That the pathological process in this disorder affects primarily the cell bodies or axons of the retinal ganglion cells is indicated by the pathological findings in the postmortem studies carried out in the last century and referred to above. The dominant finding is axonal loss and demyelination in the temporal portion of the optic nerve which we have referred to as the centrocaecal projection. Quigley *et al.* (1982) carried out a quantitative study in a single case and demonstrated that the selective damage to the temporal quadrant was accompanied by moderate axonal loss in the other three quadrants. Where the retina has been studied (*see, e.g.,* Rönne, 1910; Victor and Dreyfus, 1965) ganglion cell loss has been found around the fovea and it is not clear whether the primary insult is to the cell bodies and fibres in the retina, in the optic nerve, or both. Of particular interest is the fact that, where the dorsal lateral geniculate nucleus (dLGN) has been studied, albeit qualitatively, the pathological changes spare the magnocellular layers (Rönne, 1910; Victor and Dreyfus, 1965).

In studies of primates with optic neuropathy secondary to vitamin B₁₂ deficiency the findings are similar and it has also been shown that there is extensive ganglion cell loss (*see, e.g.,* Hind, 1972). These observations also leave open the question as to whether the primary insult is to the cell body or the axon.

There is some evidence that the ganglion cell bodies or axons may be damaged before entering the optic nerve: a higher incidence of abnormalities of the b-wave of the electroretinogram may occur in toxic amblyopia than in disorders known to affect primarily the optic nerve (*see, e.g.,* Ikeda *et al.*, 1978); there is fluorescein angiographic evidence for a vascular abnormality of the inner retina (Frisén, 1983), although such abnormalities may be a consequence of delayed axoplasmic transport at the level of the cribriform plate; magnetic resonance imaging of the optic nerve is a sensitive indicator

of optic nerve damage in optic neuritis and Leber's optic atrophy but a recent study has failed to reveal any evidence of an abnormality in early cases of tobacco-alcohol amblyopia (Kermode *et al.*, 1989). The mechanism of the neuronal damage in tobacco-alcohol and other toxic amblyopias is unknown but most workers in recent years have considered the high cyanide levels in the blood of such patients to be of aetiological significance, perhaps in combination with vitamin deficiency and hepatic dysfunction. These arguments have been recently reviewed, for example, by Foulds and Pettigrew (1977) and Jestic *et al.* (1984).

The second important evidence which must be considered is the fact that the earliest part of the field to be affected, and the densest portion of an established caecocentral scotoma, is invariably found between the fixation point and the blind spot (*see, e.g.*, Traquair, 1947 and fig. 1). It is therefore in this retinal region, or its projection in the optic nerve, that an explanation for the relative susceptibility of the CCP must be sought, the FP being considered as the next most vulnerable. It is true that depressed function can be found in regions of the visual field outside this zone (*see, e.g.*, Foulds, 1981) in agreement with the quantitative pathological study of Quigley *et al.* (1982). The difference in vulnerability between the CCP and other retinal projections is not absolute but is of such a degree as to be clearly demonstrated in the studies of those advanced cases of toxic amblyopia as have come to autopsy, particularly in the 10 dLGNs studied by Rönne (1910).

An appreciation of the origin of the concept of the 'papillomacular bundle', the demonstrations of the fibre anatomy of this projection shown in figs 2–5, the density of the capillary circulation in the ganglion cell layer shown in fig. 6, and recent advances in the understanding of the anatomy of the inner retinal layers and optic nerve, have permitted us to consider critically the possible explanations for the susceptibility of this region of the visual field in toxic amblyopia and related disorders.

The 'direct access route' of the foveal fibres

It has been suggested that the unique rectilinear projection of the foveal fibres may be an important distinction from the projection of other retinal regions. However, the result shown in figs 3–6 show clearly that it is only some fibres originating in the nasal hemifovea that project directly; most of the foveal ganglion cell axons pursue increasingly curvilinear courses at increasing distances from the horizontal meridian. It is not possible, on the basis of the architecture of the nerve fibre layer between the fovea and the disc, to distinguish between the boundaries of the foveal projection and the arcuate bundles on either side originating in extrafoveal retina.

Fibre size

A commonly held suggestion has been that the susceptibility of the fibres subserving the central visual field in a variety of disorders is that the axonal diameters of these fibres is smaller than those subserving peripheral retina. Whilst it is certainly the case that in general terms receptive field size, ganglion cell soma size and axonal diameter increase with eccentricity (*see* Stanford, 1987, for recent measurements based on conduction velocities) it appears that the variation in fibre diameter within the central 15° of the visual field may be less marked than has been thought.

Many optic nerve fibres have diameters of 1 μm or less and measurements cannot

be made accurately using light microscopic techniques. Furthermore, without tracer techniques it is extremely difficult to know precisely the retinal origin of fibres observed in the optic nerve. Until recently the available information came from an indirect method of study employed by Potts *et al.* (1972) in which the fibre diameter spectrum of a normal primate optic nerve was compared with the result obtained following the production of a foveal retinal lesion. Ogden (1984), however, has examined by electron microscopy nerve fibre size spectra in retinal nerve fibre bundles of the cynomolgus monkey. The mean diameter of fibres in 44 bundles in the centrocaecal region sampled within 1 mm of the optic disc was 0.4 μm , in 38 arcuate bundles was 0.6 μm and in 30 nasal bundles (from nasal peripheral retina) 0.8 μm . A major difference seemed to be that the FP lacked fibres larger than 2.5 μm in diameter.

Of greater relevance to the present discussion, however, is the fact that the axonal diameter of a ganglion cell situated in the retinal region between the optic nerve and the optic disc will not differ significantly from that of a ganglion cell of the same type, at the same eccentricity temporal, superior or inferior to the fovea. Whereas this has not been demonstrated directly (it would be extremely difficult to do so) Ogden has also shown (his fig. 7) that as the fascicles of the FP approach the disc they are joined by the larger diameter axons of the ganglion cells subserving the retinal region between the fovea and the disc; hence the relationship between axonal diameter and ganglion cell eccentricity is the same between the fovea and the optic disc as in any other direction from the fovea.

Cell types

It must be considered that regional variations in the distribution of cell types may account for the vulnerability of the central retinal projection, particularly in view of the evidence that in toxic amblyopia the parvocellular projection may be selectively vulnerable (Rönne, 1910; Victor and Dreyfus, 1965); it has been stated by a number of authors (*see, e.g.*, Derrington and Lennie, 1984) that the central fovea may be devoid of the largest class of ganglion cell which has been called the $P\alpha$ cell (Perry *et al.*, 1984; Perry and Cowey, 1985) by analogy with the α cell originally described in cat retina (Boycott and Wässle, 1974) and more recently the M cell in view of its destination, the magnocellular layers of the dLGN (Shapley and Perry, 1986). However, it may be that the apparent lack of M cells in the fovea is an artefact of the sampling bias introduced by microelectrode recording from the retina (*see* Perry and Silveira, 1988) and histological studies of the distribution of the major classes of ganglion cell show the ratio of P and M cells to be constant across the retina (Perry *et al.*, 1984).

The only known characteristic of the distribution of ganglion cell classes which is not uniform (at least within the central 40°) is the central retinal zone in which the P cells have dendritic field sizes which do not vary with eccentricity. These correspond to the midget ganglion cells described by Polyak (1941, 1957) and are largely found within the central 10° (or 2 mm). More peripherally the morphology of P cells changes and a typical increase in dendritic field size occurs with eccentricity. However, this inhomogeneity in retinal organization is concentrically distributed about the fovea at low eccentricities and does not correspond to the distribution of ganglion cells making up the CCP. In experimental acrylamide-induced toxic visual pathway damage in primates a similar P cell vulnerability has been demonstrated (Merigan and Eskin, 1986).

Ganglion cell density

In one important respect the organization of the ganglion cell layer of the retina is not radially symmetric and this is the variation in ganglion cell density which falls off at a lower rate along the nasal horizontal meridian than in any other direction, resulting in isodensity contours which are egg-shaped and elongated in a nasal direction (Perry and Cowey, 1985). However this density difference becomes prominent only outside the central 15° and cannot be relevant to our discussion.

The fibre density of the nerve fibre layer

It has also been suggested that the fibres of the CCP are more densely packed than the projections of other retinal regions and that for this reason they may be more vulnerable to a metabolic insult than other ganglion cell axons. There have been a number of recent studies investigating this quantitatively and whilst there is some disagreement regarding the absolute values of the thickness of the optic nerve fibre layer there is good agreement regarding the relative differences between different projections to the optic nerve. The thickness of the nerve fibre layer of the primate eye increases along the horizontal meridian from the fovea to the optic disc but nowhere does the thickness become as great as that in the arcuate bundles coursing above and below the FP to reach the poles of the optic disc (Radius, 1980; Ogden, 1983a). Typical examples would be a thickness of greater than 150 μm for the arcuate bundles as they reach the disc and around 60 μm for the bundles originating in centrocaecal retina. Ogden (1984) has also demonstrated that the total fibre content of a typical arcuate bundle close to the disc increases to, for example, 18 000 fibres to be compared with around 13 000 fibres in a sample papillomacular bundle.

Radius (1980) commented on how remarkably thin the nerve fibre layer is in this region (the CCP), a finding which was unexpected in the light of the prevailing view in much of the clinical literature that this part of the retina is occupied by a discrete, densely packed papillomacular 'bundle'. Radius suggested that most axons subserving central vision must follow an arcuate pattern and indeed our fig. 4 demonstrates that even as far as the nasal hemifovea is concerned the superiorly and inferiorly situated ganglion cells seem to 'avoid' the nasal horizontal meridian. The fact that the fibres from foveal ganglion cells avoid the region of the retina directly between the fovea and optic disc is clearly advantageous to the organism from an optical point of view. In the same sense that the inner layers of the retina are displaced at the fovea, thus avoiding the formation of a capillary bed over the most visually sensitive part of the retina, it appears that the fibres have avoided a region of retina at the expense of the arcuate regions.

The glial content of nerve fibre bundles

The nerve fibre bundles in the retina are separated by elongated processes of Müller cells (Radius and Anderson, 1979). Ogden (1983b) has shown that the glial content of retinal nerve fibre bundles is at least 18% of the cross-sectional area and much of this originates from the Müller cells which may be of importance with respect to the function of the axons (*see, e.g.,* Nicholls and Kuffler, 1964). Glial tissue of astrocytic origin, on the other hand (within retinae and across species), is closely related to the presence of blood vessels in the inner retinal layers (Stone and Dreher, 1987) and may not be of such direct functional importance to the neural elements of the retina. Apart

from this consideration, Ogden (1983*b*) has shown that the glial content of the papillomacular and of the arcuate bundles does not differ significantly.

Hind (1972) has argued that a difference in the glial content of the temporal portion of the optic nerve might be of aetiological significance. Radius and Gonzales (1981) have studied the optic nerve of human eyes at the level of the lamina cribrosa and found a greater density of connective tissue and glial cell processes in the nasal and temporal as opposed to superior and inferior sectors, although the precise distribution varied between individuals. At this level there is no evidence for a relative lack of glial elements in the region of the nerve corresponding to the CCP.

The caecocentral projection within the optic nerve

A comprehensive description of the distribution of axon diameters across the primate optic nerve has also only recently become available (Reese and Ho, 1988). Unlike the measurement in the nerve fibre layer discussed above it is not possible to know the retinal origins of the axons studied beyond an approximation. This study has confirmed in general terms the preponderance of small calibre axons in the centrottemporal regions of the optic nerve demonstrated in light microscopic studies (*see, e.g., Potts et al., 1972*). Immediately behind the eye this is also the case at the temporal margin of the nerve and this must represent the projection of the fovea and caecocentral retina. However, Reese and Ho (1988) stress that there are no anatomical features which distinguish this region of the nerve as a clearly demarcated 'bundle' either on the basis of the fascicular architecture or axonal diameter. Some larger diameter axons are found in this region of the nerve and similar fine diameter axons are found throughout. Any conclusions that can be drawn from this evidence are limited by the extent to which retinal topography is preserved in the optic nerve and although the classical concept of a precise topographic representation has been questioned in the cat (Horton *et al.*, 1979) the most recent evidence confirms a tighter topography in the macaque (Naito, 1989). Naito (1989) has also confirmed the observations from evidence such as that shown in fig. 2 that the CCP migrates to the centre of the optic nerve and occupies that position up to the chiasm. Temporal parafoveal retina, however, projects to the periphery of the nerve and remains in the periphery.

If we consider the effect of damaging every axon with a diameter below some arbitrary value the field defect produced would be predominantly central, without a sharply defined margin, and certainly symmetrically distributed about the fovea and not caecocentral. However, a lesion restricted to the temporal portion of the anterior optic nerve, or the centre of the nerve posteriorly from several mm behind the globe to the chiasm will result in a caecocentral scotoma.

Regional variations in the vasculature of the inner retinal layers

Michaelson (1954) first clearly demonstrated that the vasculature of the inner retina consists of three layers. The details of the architecture have been clarified recently by Henkind and others (*see, e.g., Henkind 1967; Shimizu and Ujiie, 1978; Iwasaki and Inomata, 1986*). The superficial capillary layer is situated at the same level as the retinal artery and vein, the precapillaries and the retinal ganglion cells. This layer is present throughout the retina and exists as a single layer in the far periphery. In the remainder of the retina a second layer is present between the inner nuclear layer and the outer

plexiform layer (the deep capillary net). At the posterior pole the superficial layer becomes increasingly 'three dimensional' as capillary loops run at the superficial boundary of the inner nuclear layer instead of being confined to the level of the precapillaries. Where the nerve fibre layer is thickest a further innermost layer, the radial peripapillary capillary net, is found. All layers form extensive vertical anastomoses.

The radial peripapillary capillary net is deficient in the papillomacular region (except close to the disc where the nerve fibre layer is thickest), but extremely well developed in the arcuate bundles above and below the foveal projection. We have considered the possibility that this arrangement may account for the vulnerability of the projection of this region of the retina. The appearance is very striking in retinal whole mounts—there is a dense capillary network at the posterior pole which excludes the caecocentral area (*see, e.g., fig. 5 of Shimizu and Ujiie, 1978*).

However, we have considered that a more significant comparison is along the horizontal meridian between retinal regions at the same eccentricities on either side of the fovea as shown in *fig. 7*. In this case we have compared retinal areas which are similar in terms of ganglion cell density, nerve fibre layer thickness (thin) and capillary density in the nerve fibre layer (sparse). The capillary density of the superficial capillary layer does not differ significantly at a given eccentricity and yet the area nasal to the fovea is vulnerable in toxic amblyopia whereas the area temporal to the fovea is not.

Quite apart from this evidence it is unlikely that the radial peripapillary network of capillaries contributes significantly to the nourishment of the ganglion cell layer. The density of this network is related very closely to the thickness of the nerve fibre layer and is probably necessary because the superficial capillaries are no longer able to supply both the ganglion cell layer and the optic fibre layer. This assertion has been supported by the work of Iwasaki and Inomata (1986) who have demonstrated that the dominant vertical position of the superficial capillaries is modified according to the thickness of the ganglion cell layer. Where this is greater than 45 μm at the foveal margin the capillaries are found in the centre of the ganglion cell layer, where it is thinner than 45 μm either at its inner or outer border. This suggests that the capillaries cannot nourish ganglion cells at a vertical distance greater than 45 μm , a figure which agrees well with the width of the capillary mesh measured in whole mounts.

Hence we have two major reasons for rejecting the suggestion that the absence of the radial peripapillary net in the papillomacular areas may be relevant to its vulnerability in toxic amblyopia. The first is that the network is only well developed where the nerve fibre layer is thicker than 40 μm and it is unlikely that at the vertical distances involved it contributes significantly to the ganglion cell layer. Secondly, when we compare retina loci along the horizontal meridian we do not find a difference in capillary circulation between retinal locations that differ markedly in their vulnerability in toxic amblyopia.

The distribution of precapillaries

If the pathological process does affect primarily the retina and if a more critical oxygenation in the local capillary circulation may be significant in the pathogenesis then it should be borne in mind that the major branches of the central retinal artery and vein course in the arcuate bundles. From the smaller arterioles and venules which run from these vessels arise the precapillaries which supply the superficial capillary net. The larger arterioles approach the horizontal meridian in temporal retina, but in the papillomacular

area such larger vessels are scarce and it seems likely that the length of the capillary portions between the arterioles and venules may be greater in the caecocentral area than in other retinal regions at a given eccentricity. Capillary density in all retinal regions increases with increasing distance from the nearest arteriolar precapillary (Michaelson, 1954), suggesting that this is an important variable. Therefore the capillary supply may be less efficient in caecocentral retina despite its apparently adequate capillary density.

We suggest that this possibility should be pursued although we have no direct evidence concerning its validity. One particular indication that this suggestion may be significant is the observation that, in humans, there is a 10–15% incidence of a branch of the ciliary circulation (the cilioretinal artery) supplying this region of retina and the macula. A difficulty in our own primate material is that we have found the details of the vascular architecture at the level of the larger vessels (unlike capillary density) to show considerable individual variability, as in humans, and we therefore do not consider it appropriate to settle this issue by a study of the nonhuman primate.

CONCLUSIONS

We suggest that the term 'papillomacular bundle' be abandoned for the reasons given above. The projection of the central 5° of the visual field should be referred to as the 'foveal projection' and the projection of the retinal area corresponding to the caecocentral type of scotoma be referred to as the 'caecocentral projection'. We further suggest that many possible explanations for the vulnerability of the caecocentral projection in toxic and tobacco-alcohol amblyopia can be rejected on critical evaluation based on the most recent anatomical evidence. Direct answers should be sought to the following questions. (1) Is the relationship between eccentricity and ganglion cell axonal diameter the same in caecocentral parafoveal retina as in temporal parafoveal retina? (2) Is there a significant overlap in the axonal diameter distributions of P and M cells? In other words are the axon diameters of M cells in central retina larger than the diameters of the largest peripheral P cells? Only if there is no overlap between these two populations can it be assumed that axon diameter alone determines the difference in the susceptibility of the P and M cell populations in toxic amblyopia. (3) In experimental models of toxic damage to the visual pathways in primates (Merigan and Eskin, 1986) evidence for a susceptibility of the CCP should be looked for. (4) Is the distribution of precapillaries in human retina significant in lowering the efficiency of the capillary supply in caecocentral retina? (5) In the nerve itself a mechanism should be sought which would accentuate damage regionally (temporally in the anterior nerve or centrally in the posterior nerve) rather than by fibre size or type. Above all we wish to stress that whether the explanation for the vulnerability of the CCP lies in the anatomy or elsewhere, future studies must address the problem of the CCP directly: it is the clarification of this problem that has been our major objective in this article.

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THE DISTRIBUTION OF MUSCLE WEAKNESS IN UPPER MOTONEURON LESIONS AFFECTING THE LOWER LIMB

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SUMMARY

To determine the distribution of weakness in the lower limb after upper motoneuron lesions the strength of 8 muscle groups was measured. Four groups of patients were studied: 22 control subjects, 16 patients with unilateral leg paresis, 4 patients with severe unilateral paralysis and 5 patients with paraparesis. In the testing posture (seated), patients with cerebral upper motoneuron lesions showed no selective loss of power in flexors or extensors on the contralateral side. Gravitational torques were included in the measurements. However, proximal muscles (acting at hip and knee) were significantly less severely affected than more distal muscles (acting at ankle and hallux). At any particular joint, physiological flexors and extensors were affected equally in both the hemiparetic and paraparetic subjects. As in the upper limb (Colebatch and Gandevia, 1989), the strength of muscles on the clinically unaffected side was reduced compared with control subjects, although no muscle groups were especially affected.

INTRODUCTION

'Upper motoneuron' lesions of the nervous system are lesions of motor cortex or descending pathways above cranial motor nuclei or anterior horn cells in the spinal cord. They are characterized by weakness, increased muscle tone and tendon reflexes and the Babinski sign. Knowledge of the distribution of weakness is generally the result of careful clinical observation of many patients. Usually there is sparing of the muscles of the upper face, mastication, those of the trunk and respiration (Jackson, 1865; Bastian, 1886; Gowers, 1893; Willoughby and Anderson, 1984), presumably because these muscles are bilaterally innervated from the motor cortex (Broadbent, 1866; Gowers, 1893). Gowers (1893) thought that distal muscles were more affected than proximal muscles in upper and lower limbs. Wernicke (1889) and Mann (1895) felt that extensors of joints in the upper limbs were more affected than flexors. Conversely, in the lower limb, flexors of joints were described as being more affected than extensors (e.g., Wernicke, 1889; Lance and McLeod, 1981), a view supported by studies of motor cortical stimulation in primates (e.g., Chang *et al.*, 1947; Lewis and Brindley, 1965). Dorsiflexors of the ankle and toes are considered as physiological flexors whereas plantarflexors are physiological extensors.

Assessment of the distribution of weakness is important in initial evaluation of patients with acute or chronic weakness of the limbs. Decisions about the likely location of lesions in the central or peripheral nervous system and the appropriate ordering of investigations

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are influenced by the distribution of weakness. In a recent study of hemiparesis (Colebatch and Gandevia, 1989) the distribution of weakness in the upper limb was assessed by measurement of voluntary strength in 11 muscle groups. Distal muscles were slightly more affected than proximal ones but upper limb extensors were not found to be more affected than flexors (*see also* Colebatch *et al.*, 1986). There was considerable variation in the relative weakness of individual muscles, particularly for an intrinsic muscle of the hand (first dorsal interosseous).

In this study we examined the distribution of strength in 8 muscle groups of the lower limbs in normal subjects and of both the weak and clinically unaffected limbs in patients with defined unilateral upper motoneuron lesions. A smaller group of patients with paraparesis due to spinal lesions was also examined because, in these patients, the weakness conforms clinically to the classical 'pyramidal' pattern.

METHODS

The maximal voluntary strength of muscles of both lower limbs were measured in normal control subjects, hemiparetic and hemiplegic patients and a small group of patients with paraparesis. Details of the patients are given in the Appendix. The control subjects were healthy and had no history of illness that could potentially affect power in the lower limbs. None participated in sports requiring strength training and most were purely sedentary. The general criteria for patient selection, testing procedures, and data analysis were comparable to those adopted in a previous study of upper limb strength (Colebatch and Gandevia, 1989). Ten females (mean age 58.5, range 18–75 yrs) and 12 males (mean age 48.3, range 21–77 yrs) were tested. The group of patients with apparently 'unilateral leg' weakness due to an upper motoneuron lesion consisted of 8 females (mean age 61.6, range 17–79 yrs) and 8 males (mean age 46.5, range 20–76 yrs). Patients with a history of a previous stroke were excluded. Most patients also had some weakness of the arm on the affected side. The responsible lesions were in the contralateral basal ganglia, internal capsule or cerebral cortex, rather than at brainstem or spinal cord levels where it may be difficult to be certain of the absence of a milder abnormality on the 'unaffected' side. Almost all had increased reflexes and a Babinski sign in the weak leg but spasticity was never severe. All but 3 were recovering from an acute lesion and undergoing active rehabilitation. They had to be cooperative, had to have good comprehension and the experimenters had to be confident that muscle groups could be strongly activated during a conventional examination of muscle power. Patients with unilateral weakness were regarded as 'plegic' if they had no clinically detectable movement in 2 of the 4 joints examined in the lower limbs (hip, knee, ankle, metatarsophalangeal joints). Patients were regarded as 'paretic' if they had detectable movement at 3 or more of the lower limb joints. This arbitrary division was similar to that used in the study of strength in the upper limb (Colebatch and Gandevia, 1989). In addition 5 subjects with paraparesis were studied, all had increased tendon reflexes below the level of the lesion and a Babinski sign on one (2 patients) or both (3 patients) sides. Two patients had cervical lesions and 3 had thoracic lesions; there were three females and two males (*see* Appendix).

Muscle strength was measured with myometers specially designed for the following muscle groups: hip flexors and extensors, knee flexors and extensors, ankle dorsiflexors and plantarflexors, and dorsiflexors and plantarflexors of the hallux. Results were calculated as torque (Newton-metres, Nm) about the joint. The force was measured at the point of contact between the limb and the myograph and then converted to torque using the distance between the contact point and the axis of the joint under study (using fixed anatomical landmarks). The degree of external restraint varied for the different muscle groups and is described in more detail below (*see* fig. 1). Because, for some muscles it is possible that forces could be registered by 'trick' movements or 'transmitted' forces, one experimenter watched the patient and disqualified contractions in which remote synergists were used. A digital storage oscilloscope displayed the force generated during each contraction (time base: 0.5 s/division). For each muscle group at least 3 maximal voluntary contractions of 3–5 s duration were attempted. Further contractions were recorded if the peak in the last contraction exceeded those before by more than 10%. The peak force obtained within the first 2 s of the contraction was taken as the estimate of maximal voluntary strength and in 80–90% of contractions

the peak occurred within the first 2 s. This time-dependent criterion was not used in the previous study of upper limb strength (Colebatch and Gandevia, 1989) and it was adopted here because preliminary studies revealed that peak forces obtained after 2 s usually reflected 'trick' movements involving remote muscles. In other studies in which we have employed twitch interpolation the true maximal force was usually achieved within the first 2 s of contraction even for a lower limb muscle (e.g., Gandevia and McKenzie, 1988). Loud verbal encouragement was always provided and oscilloscope feedback was available for all contractions. The greatest value obtained from the 3 (or more) efforts was used in subsequent analysis.

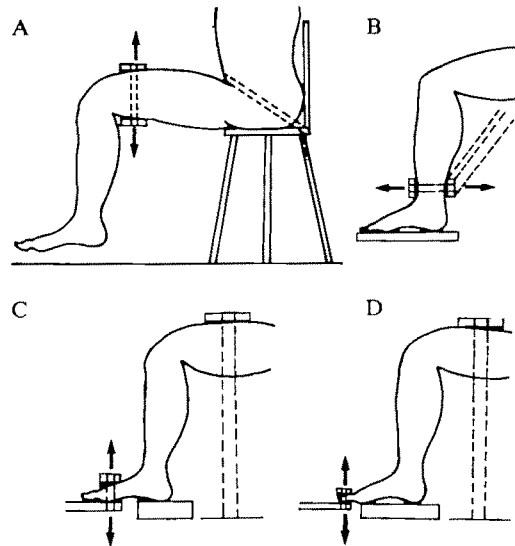


Fig 1. Diagrammatic representation of the experimental methods used to measure strength of muscle groups in the lower limbs. Myometers consisted of steel bars with strain gauges bonded to their bases. The subject either flexed or extended the hip thus either pulling upwards or pushing downwards on the bar (A). The subject either extended or flexed the knee (B), pushing forwards or pulling backwards on the bar. The subject dorsiflexed or plantarflexed the ankle (C), thus pulling upwards or pushing downwards on the bar. The height of the knee was fixed with a steel bar running transversely across the thigh. The subject either dorsiflexed or plantarflexed the hallux (D). The block under the subject's foot was carefully placed so that the analysed movement was at the metatarsophalangeal joint. Again, the knee was rigidly clamped. For all tests the arms were comfortably folded.

Different techniques and precautions were required for contractions of each muscle group (fig. 1). During the testing of power at all joints the leg that was not being examined was partly extended at the knee with the foot relaxed on the test plate. It was not possible to mimic the postures commonly used in clinical testing for the hip and knee because the subjects had to be restrained in the seated position so that all 8 muscle groups could be tested. The aim was to isolate the muscle group being studied so that other muscles could not contribute to the measured force. For all muscles the subject was comfortably seated in an upright rigid chair which was bolted to the floor and to the steel base-plate of the myometers. Power of hip flexion and extension was measured with the thigh at about $85-90^\circ$ to the trunk, with the leg dependent just above the ground (fig. 1A). The lower thigh was encircled in a clamp to which the strain gauges were attached. Knee flexion and extension were tested with the leg at 90° to the thigh and the foot in the usual posture when seated (fig. 1B). The myometer was connected to the subject about 3 cm above the medial malleolus. For hip and knee movements the subject was stabilized in the chair with a wide strap at waist level. In addition, downward pressure was applied to the subject's shoulders. This was particularly necessary for hip extension to minimize lifting of the subject from the chair. Dorsi- and plantarflexion of the hallux were examined with the ankle and toes in the normal resting position (i.e., 180° to the line of the foot).

To examine movements at the ankle and metatarsophalangeal joint of the hallux it was necessary to immobilize the flexed knee using a heavy rigid clamp which was forced over the distal femur. This reduces the contribution from the gastrocnemii on ankle torque. For ankle torques the leg was vertical and the foot 90° – 100° to the lower leg. Ankle plantarflexion was the most difficult movement of all to isolate successfully. It was essential that the subject attempted to depress the ball of the foot without elevation of the heel. For the ankle forces the foot was restrained with a wide clamp (4 cm width) just proximal to the level of metatarsophalangeal joints. Given that the ankle plantarflexors may be difficult to activate fully with voluntary effort based on twitch interpolation (e.g., Belanger and McComas, 1981; Bigland-Ritchie *et al.*, 1986) it is possible that the values for ankle plantarflexion obtained here, and in clinical examination underestimate the optimal muscle force. However, the values for plantarflexor torque were reproducible within a testing session (fig. 2). They showed acceptable variability as judged by reproducibility between sessions (*see Results*) and by comparison with values reported by others (e.g., Viitasalo *et al.*, 1980). For movement at the hallux the distal phalanx was clamped with the foot in the usual resting position. It was sometimes necessary to abduct the lateral 4 toes to prevent them touching the myometer. The heel rested on a block at the same height as the myometer for studies of the ankle and toe.

During the course of each study the 'weight' of the thigh, foot and hallux was measured using the usual myometer and limb restraints. These gravitational forces were later added to those obtained for hip flexion, ankle dorsiflexion and toe dorsiflexion. This was especially important for calculation of the hip flexor and ankle dorsiflexor torques and is not routinely considered in many assessments of muscle force.

The right side was usually studied first in normal subjects and the stronger side was measured first in patients. Because of the physical constraints of the myometers and clamps the same testing sequence was used for each study: hip (flexion then extension), ankle (dorsi- then plantarflexion), hallux (dorsi- then plantarflexion) and knee (flexion then extension). The testing required a minimum of 48 maximal voluntary contractions. However, the 'testing' chair was designed so that minimal movement of the trunk was required between testing strength at different muscles and on the two sides. Thus the full sequence of tests was usually completed in less than 2 h.

Statistics

Different subsets of data were analysed using *t* tests, and two-way analyses of variance with Duncan's multiple-range test. Nonparametric tests included the sign test and Spearman's rank correlation. Statistical significance was set at the 5% level.

RESULTS

Normal subjects

The strength of the 8 muscle groups was measured for both the right and left sides (Table 1). Fig. 2 illustrates the profiles of the force recorded in a normal subject and it shows the reproducibility of peak forces during an experimental session. There was a significant difference between the two sides ($P < 0.05$, paired *t* test) for 3 muscle groups in males and 1 in females. Right hip flexion, left knee flexion and right toe dorsiflexion were stronger than the contralateral muscle group in males, whereas right hip extension was stronger than the left in females. With the exception of hip flexion in males, these differences were relatively small ($< 20\%$). Mean strength of right hip flexion in males was 177 Nm (± 30 , SD), 30% greater than for the left hip 134 Nm (± 22 ; $P < 0.01$). This difference was also present for each session in 3 subjects studied on 4 occasions (*see below*). Values for hip flexion on the right and left sides are also given in Table 1 for males. This side-to-side difference has been preserved in comparisons with data from patients.

When expressed as joint torque the muscles of the hip were clearly the strongest in both sexes while toe muscles were the weakest. In contrast to the upper limb in which the flexors of elbow, fingers and thumb are stronger (by 2–3.5 times) than their

TABLE 1 NORMAL SUBJECTS MAXIMAL TORQUES FOR LEG MUSCLES*

		<i>Hip</i>		<i>Knee</i>		<i>Ankle</i>		<i>Hallux</i>	
		<i>Fl</i>	<i>Ex</i>	<i>Fl</i>	<i>Ex</i>	<i>Df</i>	<i>Pf</i>	<i>Df</i>	<i>Pf</i>
Females (n = 10)		93.8	82.6	29.0	23.5	36.9	34.5	1.65	1.80
		34.6	45.5	7.4	9.1	9.0	10.5	0.44	0.87
Males (n = 12)	L	134	149	62.5	61.8	64.8	86.7	3.29	4.73
	R	177							
	L	22.0	38.1	13.8	19.2	8.6	12.8	1.41	1.83
	R	30.2							

* Maximum strength (in Nm) measured for 22 healthy volunteers. Mean values are given, with SD below. Values for the right and left sides have been combined (for details, see text). Hip flexors and extensors are the strongest muscle groups in both females and males. Plantar- and dorsiflexors of the hallux were the weakest muscle group in both sexes. Fl = flexion, Ex = extension; Df = dorsiflexion; Pf = plantarflexion.

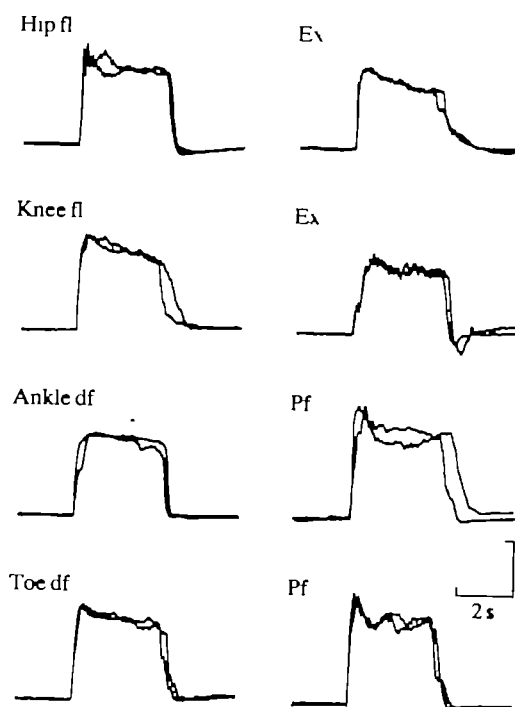


FIG. 2. Data from one experimental session to show (from above down) the forces produced by hip flexion and extension, knee flexion and extension, ankle dorsiflexion and plantarflexion, and toe dorsiflexion and plantarflexion. Two of the force profiles have been superimposed to show reproducibility. The absolute baselines were stable over many contractions but for some muscle groups there was occasional incomplete relaxation (ankle plantarflexion) or antagonist contraction when given the signal to relax (knee extension) and this altered the baselines briefly after some test contractions. Vertical calibration: 200 mV for all myographic responses except knee flexion, toe dorsiflexion and plantarflexion for which the calibration represents 400 mV. When corrected for gravitational effects and converted to joint torques the peak values were 116 and 101 Nm for hip flexion and extension, respectively, 49 and 21 Nm for knee flexion and extension, respectively, 68 and 82 Nm for ankle dorsiflexion and plantarflexion, respectively, and 2.2 and 3.4 Nm for toe dorsiflexion and plantarflexion, respectively.

antagonists (Colebatch and Gandevia, 1989), there was, by comparison, relatively little difference between the mean strengths of physiological flexors and extensors at any joint in the lower limb *in the positions in which they were tested*. The greatest difference occurred for the hallux in males, in which the mean maximal strength of plantarflexion was 1.42 times greater than for dorsiflexion. The muscles acting on the knee were weaker than those of the ankle in both sexes with this tendency being more marked in females. Strength in males was approximately twice that in females for all muscles in the lower limb. By contrast, in the upper limb, the strength difference between the sexes was slightly less marked for distal muscles (Colebatch and Gandevia, 1989). The strength difference between the sexes cannot be completely explained by the fact that the female group was approximately 10 yrs older than the male group on average. This discrepancy in age arose because the control subjects were selected to match the patient group.

Three male control subjects (ages 32, 33 and 60 yrs) had the full study performed on 4 occasions to assess the reproducibility of the procedures. The coefficient of variation was usually less than 20% for each muscle group. The mean coefficients of variation in the group of subjects (both lower limbs included) were: hip flexion, 11.0%; hip extension, 20.1%; knee flexion, 10.4%; knee extension, 14.6%; ankle dorsiflexion, 10.8%; ankle plantarflexion, 16.0%; hallux dorsiflexion, 11.0% and hallux plantarflexion, 16.2%. The values for hip extension, ankle and toe plantarflexion are greater than those for upper limb muscles measured in the same laboratory (e.g., Viitasalo *et al.*, 1980; Gandevia *et al.*, 1983). Reproducibility for hip and knee flexors, and for dorsiflexors of ankle and toe is similar to that for upper limb muscles. The important point in comparisons which follow is that the patients and normal subjects were examined under identical conditions.

Hemiparetic subjects

Sixteen patients (8 females, mean age 62, range 17–79 yrs and 8 males, mean age 47, range 20–76 yrs) were classified as 'paretic' (*see* Methods). The mean degree of strength varied from 23% to 94% of that on the normal side in the group of patients. The degree of weakness was first expressed by comparing the strength of each muscle group on the weak side with that on the stronger side (fig. 3, Table 2). This approach is similar to that used in the clinical examination to assess relative strength of a muscle group. It assumes that the ipsilateral side is of normal strength, and does not take into account possible ipsilateral effects. Averaging the degree of weakness for the 16 patients gave the following ranking for relative weakness (mean percentage residual strength is given in bracket): ankle plantarflexion (37%), dorsiflexion of hallux (38%), plantarflexion of hallux (44%), ankle dorsiflexion (45%), knee extension (51%), knee flexion (53%), hip extension (63%) and hip flexion (68%). The distribution of weakness between the muscle groups did not conform to a common pattern in different patients, nor was any single muscle group always most severely affected. However, distal muscles were commonly affected more than proximal (fig. 3). The weakest muscle group (relative to the unaffected side) in specific patients was hallux plantarflexion (5 patients), hallux dorsiflexion (1 patient), ankle plantarflexion (5 patients), knee extension (1 patient) and knee flexion (2 patients). One patient had no movement of ankle and toe plantarflexion, and 1 had no movement of ankle plantarflexion and toe dorsiflexion. Statistical analysis revealed that the differences in relative strength between leg muscles in hemiparesis

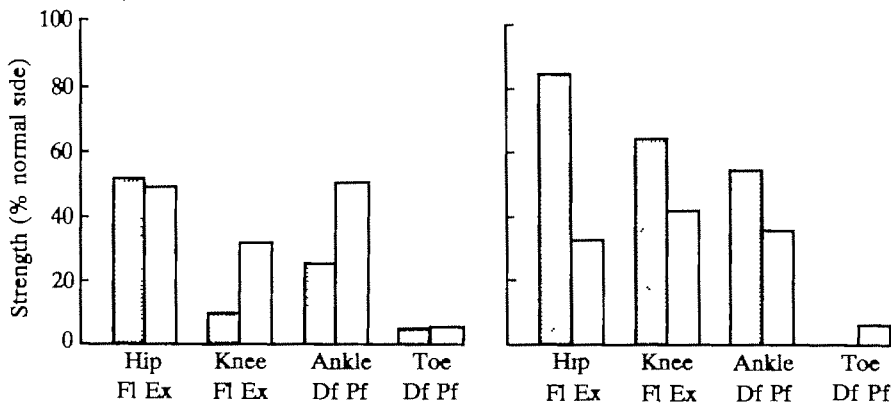


FIG. 3. Distribution of muscle weakness for 2 of the 'paretic' subjects to reveal the variability encountered. The strength of the paretic side has been expressed as a percentage of the opposite (spared) side. The muscles are denoted below the bars. Both subjects show a tendency for distal muscles to be more severely affected than more proximal muscles. Data in the left panel from a 62-yr-old man with a right internal capsule infarct. Physiological flexors of the knee and ankle were more severely impaired than the extensors of these joints, but flexors and extensors showed comparable impairment at the hip and hallux. Data in the right panel from a 53-yr-old woman with an infarct in the territory of the left middle cerebral artery. Physiological extensors of the hip, knee and ankle were more severely impaired than the flexors.

TABLE 2 HEMIPARETIC PATIENTS STRENGTH OF LEG MUSCLES*

	<i>Hip</i>		<i>Knee</i>		<i>Ankle</i>		<i>Hallux</i>	
	<i>Fl</i>	<i>Ex</i>	<i>Fl</i>	<i>Ex</i>	<i>Df</i>	<i>Pf</i>	<i>Df</i>	<i>Pf</i>
Affected side								
Females (n = 8)	65.3	51.7	12.2	12.5	14.1	10.4	0.48	0.40
Males (n = 8)	104	102	32.5	42.1	25.1	31.2	1.12	1.31
'Unaffected' side								
Females (n = 8)	90.5	76.5	22.0	23.1	30.0	35.9	1.5	1.6
Males (n = 8)	164	148	62.2	71.9	59.5	75.3	3.0	3.6

* Residual strength in hemiparetic subjects (Nm) of the 8 muscle groups on the clinically affected side above and 'unaffected' side below. Mean values are given. See also figs 2 and 3. Abbreviations as in Table 1.

were significant (ANOVA, $P < 0.01$) with extensors and flexors of the hip being least affected (Duncan's test, $P < 0.05$). Not unexpectedly, there were significantly different distributions of weakness among the group of patients ($P < 0.001$). There was no significant difference in the relative weakness of physiological flexors and extensors at any joint.

A second way in which the weakness of individual muscles can be expressed is relative to the overall mean reduction in strength for all muscles on the affected side in each subject. These data are plotted in fig. 4. This reveals that the plantarflexors of the hallux showed the greatest variation between subjects in the degree of weakness and the hallux dorsiflexors showed least variation. No muscle group in the lower limb showed the intersubject variation found for a single intrinsic muscle of the hand (Colebatch and Gandevia, 1989).

The strength of the patients on the clinically *unaffected* side has been analysed to

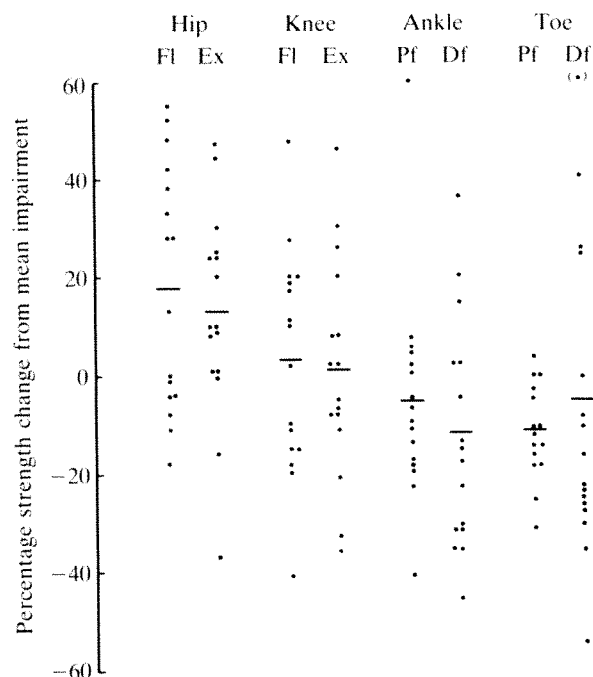


FIG. 4. Relative weakness of the 8 muscle groups for the hemiparetic subjects. The degree of weakness has been calculated (as a percentage) by using the strength on the spared side as a reference. To permit comparison between subjects, the weakness of each muscle group has been expressed relative to the overall mean weakness for each subject. Thus for each subject the more severely affected muscles lie below zero, the less affected above it. One subject does not have data points for knee flexion or extension. A value of +88% for hallux plantarflexion in 1 subject is displaced. There is a tendency for distal muscles to be more severely affected than proximal muscles, but there is no clear difference between the relative effects on flexors and extensors.

determine whether there was any strength change compared with the control population. Overall, the mean strength for all muscles on the unaffected side was 93% that of control subjects. This slight reduction was statistically significant (sign test, $P < 0.01$) but there was no tendency for specific muscle groups on the unaffected side to be particularly affected (ANOVA, $P = 0.41$). When values were expressed relative to the strength in normal subjects, the ranking of muscles on the hemiparetic side was similar to that on page 1464. The three most affected groups remained the same: hallux plantarflexion, hallux dorsiflexion and ankle plantarflexion, and the 3 least affected were hip flexion, hip extension and knee flexion (significantly different, Duncan's test, $P < 0.05$). This ranking was highly correlated with that obtained when strength of the weak side was expressed relative to the clinically unaffected side ($r = 0.90$, $P < 0.01$, Spearman's rank correlation).

Hemiplegic patients

To analyse further the likelihood of a change in voluntary muscle strength on the 'unaffected' side in upper motoneuron lesions, 4 separate patients classified as 'plegic' were studied (*see Methods*). Muscles acting on the toes and ankle were paralysed in

each subject, and 1 also had paralysis of hip flexion (but not extension). One patient was completely paralysed for all muscle groups. Strength was significantly reduced on the 'unaffected' side to a mean of 74% compared with the normal group ($P < 0.01$, sign test) but, as for the 'paretic' patients, no muscles were selectively weakened. Profiles of maximal voluntary forces from one study are shown in fig. 5 with forces on the 'plegic' side at high-gain.

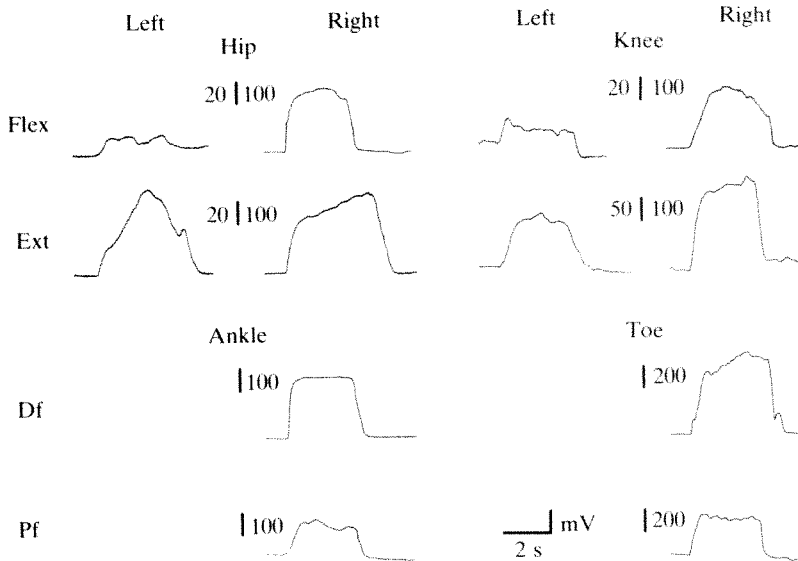
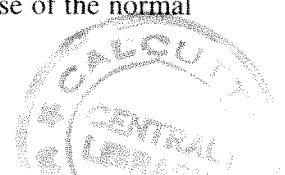


FIG. 5. Raw data collected from a 'plegic' patient, with no detectable movement at the left ankle or hallux. The patient was a 70-yr-old woman with a left hemiparesis due to a small right internal capsular infarct. Data were later converted to Nm by correction for the gravitational torques and measurement of the lever arm (see Methods). Responses shown at high gain for torques produced on the affected side.

Paraparetic subjects

Studies were performed in patients with spinal cord lesions and clinically 'classical' flexor distributions of weakness and associated reflex changes. The overall mean strength for the muscles in the paraparetic patients was 61.6% ($\pm 21.4\%$) that for the control group ($P < 0.001$). However, this reduction in strength appeared for all the muscle groups in the leg and there was no significant tendency for paraparesis to affect specific muscle groups (ANOVA, $P = 0.50$). As expected, there were differences between individual patients in the degree of weakness ($P < 0.01$). The strength of the physiological flexor at each joint was expressed as a ratio of that of the physiological extensor. Mean values (and SD) were obtained for each joint by averaging the values for both legs of all 5 patients. For the joint angles used in this study, the respective ratios were: hips (flexion/extension), 1.06 ± 0.35 ; knee (flexion/extension) 1.08 ± 0.38 ; ankle (dorsiflexion/plantarflexion), 1.16 ± 0.25 ; hallux (dorsiflexion/plantarflexion) 1.10 ± 0.29 . These ratios were statistically indistinguishable from those of the normal



population (fig. 6) so that there is no evidence for selective weakening of either physiological flexors or extensors in paraparesis.

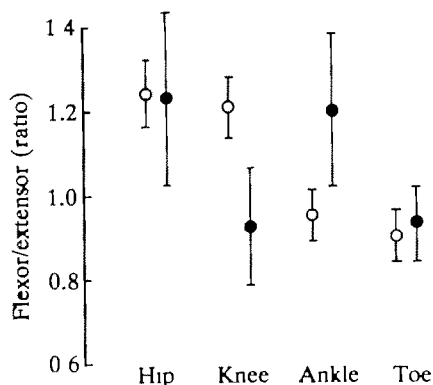


FIG. 6. Data for the ratio between flexor and extensor strength at the hip, knee, ankle and hallux for normal subjects (open circles) and patients with paraparesis (closed circles). The means ($\pm$ SEM) are plotted. For the ankle and hallux the ratio represents dorsiflexor/plantarflexor strength. At no joint were the differences in the ratio statistically different between the two groups.

DISCUSSION

The major findings of the study are as follows. First, there was a tendency for distal muscles in the lower limb to be more severely affected than proximal muscles in the 'paretic' and 'plegic' patients; secondly, physiological flexors were not affected more than physiological extensors in the testing posture; and thirdly, individual patients demonstrated no uniform pattern in the distribution of weakness (sometimes the flexor would be more severely affected than the extensor at one joint with the converse at other joints); and finally, there was a reduction in strength on the clinically 'unaffected' side in patients with unilateral lesions, with this being more marked in 'plegic' than 'paretic' patients.

Use is made in clinical neurology of the 'distribution' of a patient's weakness, namely the extent to which different muscle groups within a limb are affected. Often an initial decision as to whether the lesion is in the peripheral or central nervous system is based on this assessment. Knowledge of the distribution of weakness produced by a central or 'upper motoneuron' lesion has been derived from careful clinical assessments over a number of years (*see* Introduction). In this report we have measured the strength of 8 different muscle groups of the leg to determine the distribution of weakness resulting from an 'upper motoneuron' lesion. The leg ipsilateral, as well as that contralateral to the lesion, was examined. Hemiplegic and hemiparetic patients were selected on the basis of a single upper motoneuron lesion. The lesions were generally well visualized by radiological procedures. In the few patients in whom this was not the case, the clinical signs were such that it was clear that the responsible lesion was unilateral and above

the brainstem. No individual patient was specifically chosen because of the presence of a particular distribution of weakness on clinical examination.

Two previous studies of hemiparesis (Colebatch *et al.*, 1986; Colebatch and Gandevia, 1989) have quantified the distribution of weakness in the upper limbs. Distal muscles (particularly wrist and finger muscles) were slightly weaker than more proximal musculature. However, there was no tendency for extensors (or flexors) to be more affected, and the shoulder abductors were affected no more than adductors. Strength was examined in a group of patients with spinal cord lesions producing bilateral weakness because paraparetic patients appear to show the 'classical' flexor pattern of weakness on clinical examination. The relative strengths of flexors and extensors at the various joints in this group were not different from those of normal subjects. In addition, the trend for distal muscles to be affected more than proximal was absent.

As argued previously (Colebatch and Gandevia, 1989), it is not legitimate to equate the distribution of voluntary strength with properties of the corticospinal/pyramidal system, because of the presence of other descending motor pathways. However, it is interesting that the predominance of distal weakness of leg muscles is consistent with the well documented corticospinal connection to distal musculature for the upper and lower limb (Liddell and Phillips, 1950; Bernhard *et al.*, 1953). Furthermore, the marked weakness of ankle plantarflexion in hemiparesis may be related to the relatively high percentage of motor cortical cells in the monkey which increase their discharge during isometric plantarflexion (Sahrmann *et al.*, 1984). This may be compounded by the brief initial inhibition of soleus motoneurons produced by motor cortical stimulation in man (Cowan *et al.*, 1983) and the difficulty in achievement of maximal voluntary force in this manoeuvre in some normal subjects tested with twitch interpolation (Belanger and McComas, 1981).

Patients regarded as hemiplegic rather than hemiparetic (because they had no clinically detectable movement at 2 or more of the 4 joints) were studied to assess the degree of weakness in the leg ipsilateral to the lesion. There is a mild reduction in ipsilateral strength in the upper limb (Colebatch and Gandevia, 1989; *see also* Gowers, 1887, 1893; Brodal, 1973) and for the lower limb. It is also interesting that the loss of power on the 'normal' side is more marked for shoulder muscles and not the intrinsic hand muscles but is quite uniform for lower limb muscles studied. It was not possible to study strength in a single intrinsic muscle of the lower limb as was done in the study of the upper limb. Thus we cannot yet provide full clinical support to the anatomical evidence for a minimal ipsilateral projection to the distal extremities (e.g., Kuypers, 1987). It is possible that the weakness on the ipsilateral side, more marked in the plegic than the paretic patients, reflects loss of an effectively ipsilateral corticofugal projection to lower limb muscles. There is anatomical evidence for such projections in subhuman primates and human subjects (*see* Phillips and Porter, 1977; Kuypers, 1987). A small population of motor cortical cells which discharged only in relation to ipsilateral contraction of the long finger flexors in the monkey has recently been described (Tanji *et al.*, 1988).

In this particular study we have relied on a comparison of torques produced under identical experimental conditions as the basis for conclusions about the changes which develop with upper motoneuron lesions. Unfortunately, because the positioning of the lower limb and trunk, and the degree of external restraint influence the values for maximal isometric (or isokinetic) strength, it is not necessarily valid to compare values obtained

in different laboratories. However, the values for maximal ankle dorsiflexor and plantarflexor *torque* are similar to those of an extensive study of strength in over 500 Danes in which values are reported according to age and height (Asmussen and Heebøll-Nielsen, 1961; cf. Tornvall, 1963). With the addition of gravitational torques (for dorsiflexion) the corresponding values in their study were approximately 60 Nm and 90 Nm for average-sized males in their sixth decade for dorsi- and plantarflexion, respectively. Values for hip forces reported here may be slightly lower but the methodologies were not strictly comparable for hip extension. Values for knee extensor and flexor torques are lower in the present study than might be predicted from other studies (e.g., Asmussen and Heebøll-Nielsen, 1961; Andersen and Henckel, 1987). It is not clear how much of the difference reflects differences in testing methods and in the anthropomorphic and age characteristics of the subject populations. Comparable data for torques produced by the hallux at the metacarpophalangeal joint have not, to our knowledge, been reported by others. If, overall, the normal values reported in this study are relatively low, it may reflect our routine use of rigid couplings with minimal padding to the myographs (*see* Colebatch and Gandevia, 1989). This reduces the tendency to recruit remote muscles which can indirectly influence the recorded torque.

Why is it that, clinically, patients with upper motoneuron lesions *seem* to have greater weakness of physiological flexors than extensors of the lower limbs? In part, it is due to mechanical and psychophysiological factors during manual clinical examination of maximal voluntary power. Some of these are mentioned below. The first relevant influence, especially in the lower limb, is that of gravity. Thus, when assessed with the patient supine, elevation of the extended leg from the bed requires a great deal of strength of the hip flexors. In a weakened leg this may lead to the impression that hip flexors are more affected than hip extensors because the flexor power assessed clinically is only that which exceeds the gravitational torque. Addition of the gravitational torques to the voluntary torques corrected for this effect in our myometric measurements. The influence of gravity has been considered in this manner by others (Strauss and De Domenico, 1986; Colebatch and Gandevia, 1989). Secondly, joint and muscle mechanics can contribute to the clinical impression, particularly for hip flexion in which the clinical testing position (supine with leg extended) minimizes the contribution from iliopsoas. The effect of a change in mechanics of iliopsoas can be substantial (Clarke *et al.*, 1950). Furthermore, knee angle can markedly influence measurements of knee flexor and extensor strength (e.g., Clarke *et al.*, 1950; Haffajee *et al.*, 1972) and it also influences ankle plantarflexion strength through its effect on the length of the gastrocnemii (e.g., Clarke *et al.*, 1950) and knee flexors. A third factor, considered in the study of weakness in the upper limb (Colebatch and Gandevia, 1989), is that the intrinsically weaker extensor muscles (of thumb, finger, wrist and elbow) can definitely be overcome by the examiner and are thus predisposed to appear weak. However, this factor may be less important in the leg with the exception of the dorsi- and plantarflexors of the ankle and hallux. Finally, the complexity of the task given to the patient may contribute. Thus the strong clinical impression that the intrinsic abductor muscles of the hand are uniformly weak in hemiparesis was not borne out by myometric measurement (Colebatch and Gandevia, 1989). When tested in isolation the clinical examiner may be surprised at the residual strength in a single muscle such as first dorsal interosseous.

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APPENDIX

Clinical details of all 'paretic' patients

Unless otherwise qualified, all deficits refer to the clinically weak side.

Case (age in yrs)	Weak side	History	Duration of weakness	Examination	Investigations
M1 (20)	L	Motor vehicle accident. Required surgical procedure; suture of dura to peritoneum and an extradural drain	1½ wks	Mild weakness of proximal leg muscles, marked weakness distally. Normal power L arm. Increase in tendon reflexes in leg with an extensor plantar response. Sensation normal	CT scan: depressed fracture of R side of the vertex with some underlying intracerebral blood
M2 (40)	L	Blow to the head producing a large R parieto-occipital subdural haematoma which was drained surgically	12 yrs	Mild L hemiparesis with increased tendon reflexes and an extensor plantar response. Decreased proprioception and sensory inattention for touch	
M3 (30)	L	Motor vehicle accident. Surgical elevation of depressed fracture	1 wk	Mild hemiparesis (initially leg weakness had been severe). No reflex or sensory signs	Skull X-ray and CT scan: depressed fracture of R parietal bone near the vertex with minimal contusion and oedema

<i>Case (age in yrs)</i>	<i>Weak side</i>	<i>History</i>	<i>Duration of weakness</i>	<i>Examination</i>	<i>Investigations</i>
M4 (68)	L	Awoke with L sided weakness	1½ wks	Mild weakness of hand, hip flexors plus slight hyperreflexia. Normal sensation	CT scan: small R internal capsule infarct
M5 (62)	R	Found on the floor by his wife PH hypertension	1 wk	Expressive dysphasia, Arm paralysed. Moderate leg weakness. Increased reflexes. Equivocal plantar response	CT scan: no definite cortical abnormality. Probable infarct in L internal capsule
M6 (55)	R	Episodes of L sided amaurotic fugax for 1 yr followed by sudden loss of consciousness. On recovering consciousness a hemiparesis was present	9½ mos	Dysphasia, hemianopia, upper motoneuron facial weakness. Hemiparesis with increased tendon reflexes and extensor plantar response. Moderate sensory loss	CT scan: large frontoparietal infarct in the territory of the middle cerebral artery. Angiography: complete left internal carotid artery occlusion
M7 (22)	L	Debulking of a R glioma grade IV 5 yrs previously, with subsequent radiotherapy and chemotherapy. The tumour was again debulked 3 wks before the test	over 1 yr	Moderate hemiparesis. Increased tendon reflexes, extensor plantar response. Deficits in proprioception, two-point graphesthesia and stereognosis	Magnetic resonance imaging (1988): large semicystic R parietal lesion
M8 (76)	L	Development of L sided weakness over 3 days	5 wks	Normal cranial nerves. Dense hemiparesis. Increased tendon reflexes and extensor plantar response. Normal sensation	CT scans (when admitted and 5 wks later): both normal
F1 (53)	R	Sudden onset of weakness with dysphasia	10 mos	Receptive and expressive dysphasia. Hemiparesis affecting distal muscles more than proximal. Extensor plantar response. Some sensory deficits	CT scan: infarct in left middle cerebral artery territory (involving parietal and frontal cortex)
F2 (79)	L	Awoke one morning with mild weakness that became severe within 24 h	2 wks	Upper motoneuron facial weakness, tongue deviated to the left. Dense hemiparesis with increased reflexes. Extensor plantar response. L sided sensory inattention (touch) and proprioceptive deficit	CT scan: infarct in R temporal deep white matter

Appendix (continued)

<i>Case (age in yrs)</i>	<i>Weak side</i>	<i>History</i>	<i>Duration of weakness</i>	<i>Examination</i>	<i>Investigations</i>
F3 (79)	L	A hemiparesis following removal of a R parietal meningioma	9 wks	Upper motoneuron facial weakness. Moderate hemiparesis. Mild hyperreflexia. Extensor plantar response. No sensory abnormalities	CT scan (postoperatively): haemorrhage in R frontoparietal cortex
F4 (66)	L	Removal of R parietal meningotheial meningioma. Preoperatively had noticed a clumsy L hand. This was followed 10 days later by a hemiparesis	3 wks	Mild hemiparesis, mainly affecting finger abduction and extension, and hip flexion. No reflex changes. L sensory inattention for touch	CT scan (following development of weakness): some intra- and extracerebral haematoma plus probable involvement of cortex with tumour
F5 (17)	L	R sided headache followed by sudden onset of field defect, paraesthesiae of L side of the body, and weakness. History of classical migraine	1 wk	L homonymous hemianopia. Tongue deviated to left. Mild hemiparesis, mainly distal. Mild hyperreflexia. Extensor plantar response. Deficits of two-point discrimination, graphaesthesia, stereognosis	CT scan: two areas of infarction on right (posterior limb of internal capsule and occipital cortex). Echocardiogram: redundant anterior mitral valve leaflet
F6 (70)	L	Sudden onset of dizziness followed by collapse and hemiplegia. PH: hypertension	1½ wks	Upper motoneuron facial weakness. Tongue deviated to left. Little movement of arm, moderate weakness of leg. Extensor plantar response. Uncooperative for sensory examination	CT scan: infarct in head of R caudate nucleus, putamen and anterior limb of the internal capsule
F7 (75)	R	Found on floor, drowsy and with R sided weakness. History of hypertension and intermittent atrial fibrillation	1 wk	Upper motoneuron facial weakness. Mild hemiparesis. No sensory deficit. Extensor plantar response	CT scan: infarct in L lentiform nucleus also involving internal capsule
F8 (60)	L	L partial pneumoectomy 2 yrs before for squamous cell carcinoma. Ten mos history of headache and clumsiness of the hand. Three mos previously had removal of R parietal tumour	3 mos	Cranial nerves normal. Painful L shoulder made assessment of power difficult. Mild paresis of leg. Extensor plantar response. Impaired proprioception, sensory in attention for touch	CT scan(postoperatively): area of porencephaly in R parietal lobe adjacent to the vertex

Clinical detail of all 'plegic patients'

Unless otherwise qualified, all deficits refer to clinically weak side

<i>Case (age in yrs)</i>	<i>Weak side</i>	<i>History</i>	<i>Duration of weakness</i>	<i>Examination</i>	<i>Investigations</i>
M1 (79)	L	Gradual development of weakness over 2 days	4 wks	Upper motoneuron facial weakness. Dense hemiparesis with no movement at the ankle and hallux. Hyperreflexia and extensor plantar response. Normal sensation	CT scan: no specific lesion
F1 (70)	L	Awoke with hemiparesis. PH. insulin dependent diabetes	2 wks	Cranial nerves normal. Severe hemiparesis with no movement of wrist, hand, ankle or hallux. Hyperreflexia and extensor plantar response. normal sensation	CT scan: small infarct in internal capsule
F2 (55)	R	Awoke with L sided headache followed by tingling and weakness in R hand and leg. History of classical migraine, hypertension	½ wk	Cranial nerves normal. Mild weakness of arm. Marked weakness of leg, with no movement at the ankle and hallux. Slight hyperreflexia. Extensor plantar response. Impaired proprioception	CT scan: 4×3 cm left frontal cerebral haematoma, superficial
F3 (73)	R	Weakness developed after the removal of a L frontoparietal meningioma	2 wks	Postoperatively she had a dense L hemiparesis with no leg movement. Reflexes increased with extensor plantar response. No sensory abnormalities	CT scan (postoperatively) tumour removed but considerable oedema present

Clinical details of paraparetic patients

M1 (71)	Six yrs of progressively increasing weakness of the legs and more recently the arms	6 yrs	Mild to moderate weakness in R and L upper and lower limbs. All tendon reflexes increased, R extensor plantar response. Impaired two-point discrimination in feet	Myelogram compression of thecal sac and spinal cord at C3/4 and C4/5 levels due to cervical spondylous
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Appendix (continued)

<i>Case (age in yrs)</i>	<i>Weak side</i>	<i>History</i>	<i>Duration of weakness</i>	<i>Examination</i>	<i>Investigations</i>
M2 (60)		Progressive weakness, paraesthesiae of legs and incontinence of urine. Three wks before test had a T3 laminectomy with excision of Schwannoma arising from the T4 root	7 mos	Moderate, almost symmetrical weakness of legs with hyperreflexia and R extensor plantar response. Normal sensation	Myelogram (preoperative) obstruction at T3/4 level
F1 (62)		Three yrs of progressive weakness of legs and R arm. Weakness exacerbated by heat, hot baths and exercise. Probable diagnosis of multiple sclerosis	3 yrs	'Classical' pyramidal distribution in R leg plus weakness of L hip flexion and knee flexion and extension. Increased tendon reflexes in R arm and leg with extensor plantar response. Normal sensation	CT scan of head: normal. Cervical myelogram normal. Visual evoked responses bilaterally abnormal. CSF: oligoclonal bands present
F2 (56)		Increasing midback pain and weakness of legs. Subsequent to this test a T3 to T5 laminectomy was performed with removal of a meningioma attached to the dura posteriorly	7 mos	Moderate weakness of both legs with increased reflexes and extensor plantar responses. Sensory level for pinprick at T6	Myelogram incomplete block at T4 level
F3 (25)		Fell from a balcony sustaining crush fractures of T8 and T9 vertebrae. Decompression laminectomy performed	10 wks	Moderate weakness of both legs with increased reflexes and Babinski signs. Sensation normal	

BREAKDOWN OF THE BLOOD-BRAIN BARRIER PRECEDES SYMPTOMS AND OTHER MRI SIGNS OF NEW LESIONS IN MULTIPLE SCLEROSIS

PATHOGENETIC AND CLINICAL IMPLICATIONS

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SUMMARY

From an extensive serial magnetic resonance imaging (MRI) study in multiple sclerosis (MS) we have identified 4 cases in which disruption of the blood-brain barrier, as detected by gadolinium-DTPA enhancement, preceded other MRI abnormalities and in 1 case clinical evidence of the new lesion. This supports the view that a defect in the blood-brain barrier, and therefore inflammation, is an early and possibly crucial event in the pathogenesis of the new lesion in MS. These cases showed a marked discrepancy between MRI abnormality and symptoms. The mechanisms contributing to this disparity are discussed, and it is concluded that far from being surprising it is to be expected.

INTRODUCTION

The sequence of events in the development of the acute lesion in multiple sclerosis (MS) remains unresolved. Histological data has been inadequate as few postmortem or biopsy studies have been performed in the context of an acute relapse (Prineas *et al.*, 1987). While an inflammatory component has been recognized for many years (Dawson, 1916; Greenfield and King, 1936) its precise role remains unclear, some authors regarding it as secondary to myelin breakdown produced by an independent mechanism (Calder *et al.*, 1989), while others consider it to be pathogenetically related to demyelination (Adams *et al.*, 1985; Hafler and Weiner, 1989). Over the last 15 yrs evidence has accumulated that a perivascular inflammatory infiltrate is characteristic of the acute lesion (Adams, 1975; Guseo and Jellinger, 1975). Such perivascular inflammation has also been seen in normal-appearing white matter of the brain and in the retinal venules in the absence of subjacent parenchymal inflammation (Arnold *et al.*, 1984; Lightman *et al.*, 1987), leading to the conclusion that perivascular inflammation in MS can occur in the absence of myelin breakdown, and the suggestion that a vascular event is a necessary preliminary to the development of structural damage.

Magnetic resonance imaging (MRI) provides a noninvasive means of studying disease

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activity in MS (Young *et al.*, 1981; Ormerod *et al.*, 1987; Paty *et al.*, 1988). Gadolinium-DTPA (Gd-DTPA) enhancement signifying breakdown of the blood-brain barrier (Hawkins *et al.*, 1990) has been shown to be a consistent finding in new lesions in relapsing/remitting and secondary progressive MS (Grossman *et al.*, 1986; Miller *et al.*, 1988a; Thompson *et al.*, 1989a). Similar studies in chronic relapsing experimental allergic encephalomyelitis have shown that the enhancement seen in acute lesions only occurs at sites of active inflammation (Hawkins *et al.*, 1990). The important question regarding the evolution of the acute MS lesion is: How early does blood-brain barrier breakdown occur? We have had the opportunity to try to answer this question in the course of a serial study comparing primary and secondary progressive MS and in a study of brainstem symptomatology in demyelinating disease. Gd-DTPA enhancement was detected either before other evidence of white matter involvement or before the development of clinical signs in 4 patients. Three patients were part of a larger cohort of 12 patients with secondary progressive MS who were taking part in a study comparing the pattern and time course of enhancement in new lesions with patients who were progressive from onset (primary progressive). In the secondary progressive group multiple enhancing lesions are frequently seen, many of which do not relate to the patient's symptoms (Thompson *et al.*, 1989a). The fourth patient presented with brainstem symptoms.

METHODS

Magnetic resonance imaging

MRI was performed on a Picker 0.5T superconducting MR imager as part of a serial study in MS. Cases 1, 2 and 3 had T₂ weighted MRI of brain (SE_{2000/60}), with 5 mm contiguous slices and a 128×256 image matrix. Case 4 had T₂ weighted MRI of brain (SE_{2000/40} and SE_{2000/120}) with 10 mm slices and a 256×256 image matrix. Scanning plane in Cases 1, 2 and 3 was determined by 4 oblique pilots (transverse, coronal, sagittal and a final check transverse pilot) to ensure consistency of the imaging plane over the course of the serial study (MacManus *et al.*, 1989). All had T₁ weighted precontrast images (SE_{300/40}), followed by intravenous injection of Gd-DTPA (0.2 mmol/kg in Cases 1 and 4, 0.1 mmol/kg in Cases 2 and 3). Post Gd-DTPA images were obtained using SE_{300/40}. MRI was repeated between 10 and 14 days later in the first 3 cases and 28 days later in Case 4.

A full neurological examination was carried out at the time of each scan and disability was scored on Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Scans were examined by D.P.E.K. and B.E.K. without knowledge of the patient's clinical condition.

CASE REPORTS

All cases had clinically definite MS (Poser *et al.*, 1983) with oligoclonal IgG bands in the CSF. The first 3 cases had relapsing/progressive MS (secondary progressive) and the fourth was still in the relapsing/remitting phase. All 4 patients were studied during an acute relapse.

Case 1

A 25-yr-old female with a 6 yr history of MS and a disability score of 4.5 on the EDSS became severely ataxic with marked weakness of her left leg such that she was only able to walk a few feet. Seven days later MRI showed numerous new lesions in both cerebral and cerebellar hemispheres with a large new lesion in the right precentral gyrus consistent with her left-sided weakness (fig 1A). Twenty-seven areas of Gd-DTPA enhancement were seen, including several small areas of enhancement within the much larger region of abnormality on the T₂ weighted MRI in the right precentral gyrus (fig 1B). One enhancing region in the left frontal lobe did not correspond to any lesion on the T₂ weighted MRI (figs 1C, D). Ten days later a lesion was clearly seen on T₂ weighted MRI in the left frontal lobe (fig 1E). T₂ weighted MRI

2 months later showed that the large precentral gyrus lesion had shrunk and was now of similar proportion to the original areas of enhancement (fig. 1F).

Case 2

A 29-yr-old male who had a 3 yr history of MS and moderate disability (EDSS = 4) developed paraesthesiae in both legs with marked pyramidal weakness and a sensory level to touch and pin prick at T8. T₂ weighted MRI 7 days later showed a new lesion adjacent to the left sylvian fissure. Gd-DTPA enhanced images showed enhancement in the new lesion, in a left periventricular lesion still enhancing from 2 wks previously, and in the left internal capsule which did not correspond to any lesion on the T₂ weighted MRI (figs 2A, B). Fourteen days later a lesion was seen on the T₂ weighted MRI in this position (fig. 2C). No enhancement was seen after injection of Gd-DTPA on this occasion.

Case 3

A 54-yr-old male, who had MS for 7 yrs and now had moderate disability (EDSS = 5), developed numbness in both hands, increasing weakness of both legs with a T10 sensory level of touch and pin prick, and urinary frequency. Five days later an MRI of brain revealed 2 new lesions known from serial scans to be less than 14 days old: 1 left frontal and 1 left thalamic. There was also a possible lesion in the right posterior temporal lobe which was barely visible (fig. 3A). After Gd-DTPA, 5 enhancing areas were seen. Two lesions (left occipital and left periventricular) were already enhancing 4 wks previously; (1 was 4 weeks old and the other was an older reactivated lesion). The 2 new lesions (left frontal and left thalamic) were also enhancing. A fifth enhancing area was seen in the right posterior temporal lobe which corresponded to the faint lesion on the T₂ weighted MRI (fig. 3B). Fourteen days later this lesion was clearly visible on the T₂ weighted MRI (fig. 3C).

Case 4

A 47-yr-old man with a 4 yr history of MS developed a rapidly progressive right-sided hearing loss following a 2 wk history of vertigo and nausea when lying on the right. Examination revealed abnormal extraocular movements with saccadic pursuit and first degree nystagmus to left and right and downwards. There was reduced perception of light touch but not pin prick in the area of the right fifth nerve, mild right facial weakness and a moderate spastic ataxia of all four limbs with brisk tendon reflexes and extensor plantar responses. There was mild impairment of vibration sense at the left hallux, Romberg's test was positive and his gait was grossly ataxic. Caloric testing demonstrated a total canal paresis on the right. Audiometric testing revealed absent hearing on the right and the pure tone audiogram was equivocal on the left. The auditory brainstem responses were absent bilaterally. Over the next 7 days auditory acuity declined rapidly on the left and then slowly improved over the next 3 wks. The right ear also began to improve and had returned to normal 1 month after presentation. The auditory brainstem responses remained absent. A initial MRI showed an enhancing lesion in the right pons extending towards the root entry zone of the eighth nerve (figs 4A, B). There was also a faint lesion in the left root entry zone which was more obvious on the enhanced scan (figs 4B, C). One month later the left-sided lesion was clearly visible on the T₂ weighted scan and continued to show enhancement (fig 4D). The right-sided lesion persisted but showed less enhancement. Thus enhancement preceded the development of clinical deafness on the left.

DISCUSSION

The serial scans of the first 3 patients show that blood-brain barrier breakdown can precede the appearance of new lesions on T₂ weighted MRI (Cases 1, 2); Cases 3 and 4 show that prominent enhancement precedes the development of the marked increase in signal on T₂ weighted MRI characteristic of the established unenhanced lesion, and in the fourth case blood-brain barrier breakdown preceded the clinical expression of the new lesion. In addition a clear discrepancy between MRI abnormalities and clinical symptoms was seen in the 3 secondary progressive cases. These observations have important implications for our understanding of the pathogenesis of MS and raise questions

about the relationship between MRI abnormalities and the development of symptoms.

Do these observations help to decide if the inflammation seen in MS is a primary or secondary event? In chronic relapsing experimental allergic encephalomyelitis

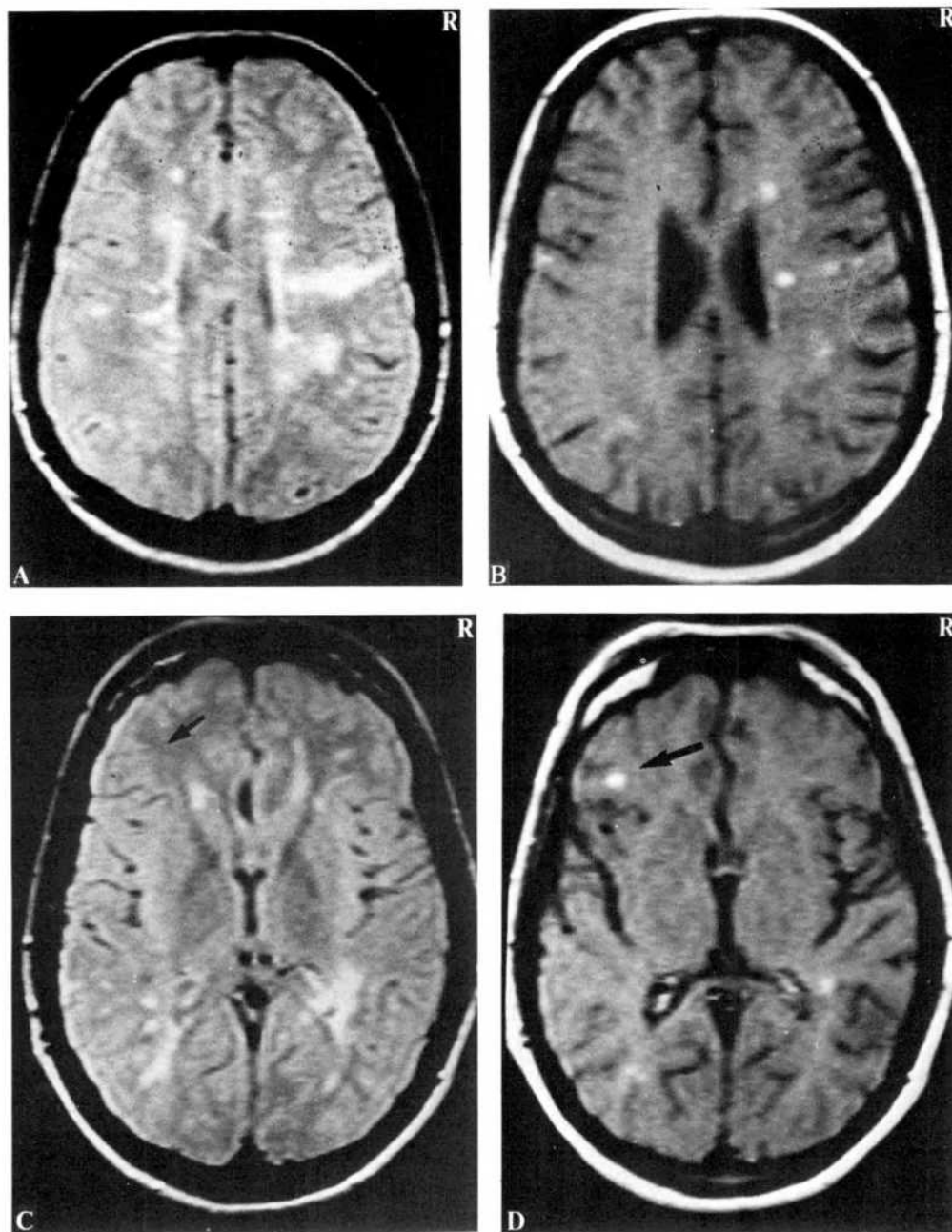


FIG. 1A-D.

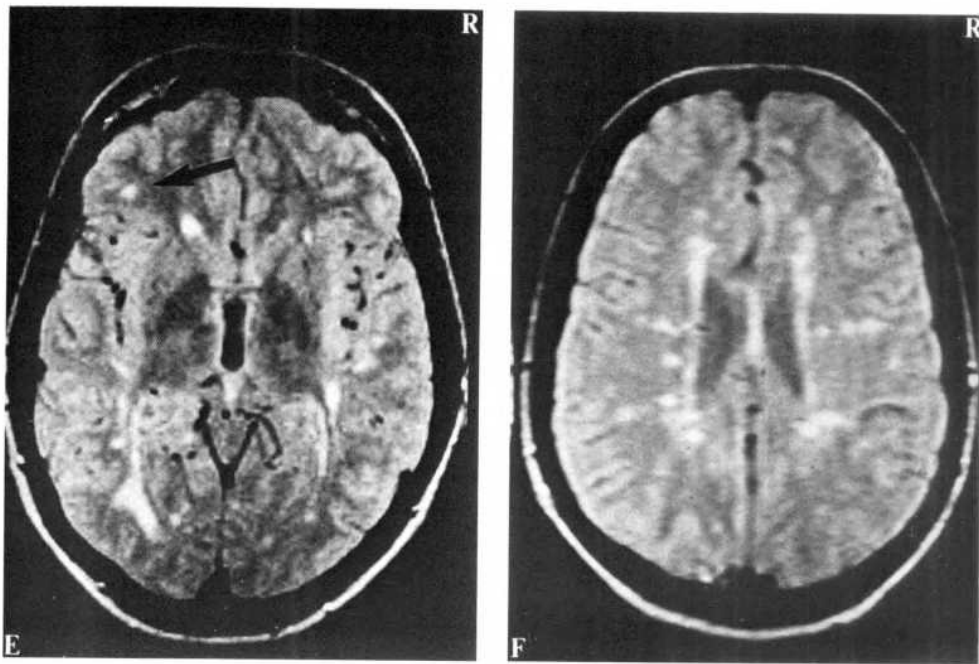


FIG. 1. A, unenhanced T_2 weighted MRI ($SE_{2000/60}$) showing a large lesion adjacent to the right precentral gyrus. B, T_1 weighted Gd-DTPA enhanced MRI ($SE_{500/40}$) several minutes later at the same level as fig. 1A showing several small areas of enhancement. C, unenhanced T_2 weighted MRI ($SE_{2000/60}$). No lesion is visible where arrowed. D, T_1 weighted Gd-DTPA enhanced MRI ($SE_{500/40}$) several minutes later at the same level as fig. 1C showing a brightly enhancing lesion. E, unenhanced T_2 weighted MRI ($SE_{2000/60}$) 10 days later at the same level as figs 1C and D. The lesion is now visible. F, unenhanced T_2 weighted MRI ($SE_{2000/60}$) 2 months later at the same level as fig. 1A showing shrinkage of the large prefrontal gyrus lesion.

(CREAE), a disease with pathological similarities to MS, enhancement with Gd-DTPA has been shown to correlate with the presence of active inflammation and occurs at the time of relapse (Hawkins *et al.*, 1990). Given the pathological parallels between the two conditions (Lassmann, 1983), it is probable that enhancement in MS is also occurring at sites of active inflammation. Furthermore, the pattern of Gd DTPA enhancement seen in acute and subacute lesions in MS (Kermode *et al.*, 1990) correlates well with the distribution of inflammation seen in pathological studies; small new lesions tend to enhance uniformly, corresponding with focal perivenular lesions, while larger older lesions show peripheral ring-like enhancement in keeping with the histological findings at postmortem of myelin breakdown products and inflammatory cells in the same distribution (Prineas and Connell, 1978). Our observations suggest that inflammation occurs very early in the evolution of the new lesion and is in keeping with the accumulating evidence that inflammation is an early and possibly the primary event in the development of new white matter change in MS.

Perivascular inflammation or cuffing in macroscopically normal appearing white matter, which had previously been considered a rare finding, is now well documented (Adams, 1975; Allen and McKeown, 1979), and more recently the crucial observation of

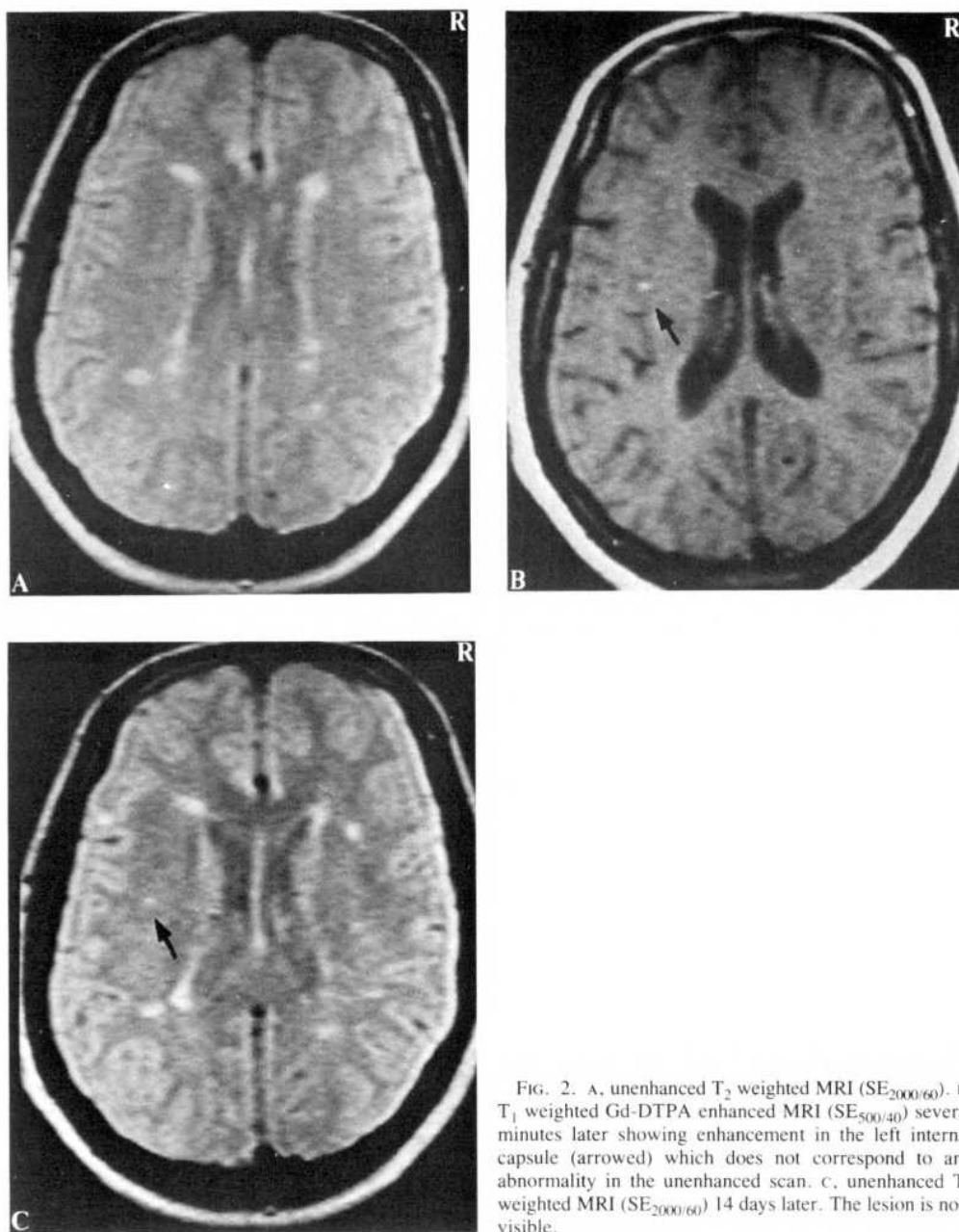


FIG. 2. A, unenhanced T_2 weighted MRI ($SE_{2000/60}$). B, T_1 weighted Gd-DTPA enhanced MRI ($SE_{500/40}$) several minutes later showing enhancement in the left internal capsule (arrowed) which does not correspond to any abnormality in the unenhanced scan. C, unenhanced T_2 weighted MRI ($SE_{2000/60}$) 14 days later. The lesion is now visible.

inflammatory infiltrate confined to the vessel wall of venules in the brain with normal surrounding tissue has been made (Adams *et al.*, 1985). This latter observation is further supported by findings in the retina of patients with optic neuritis and MS (Rucker, 1944). In this area which is free of myelin, venous sheathing has been detected in up to 25%

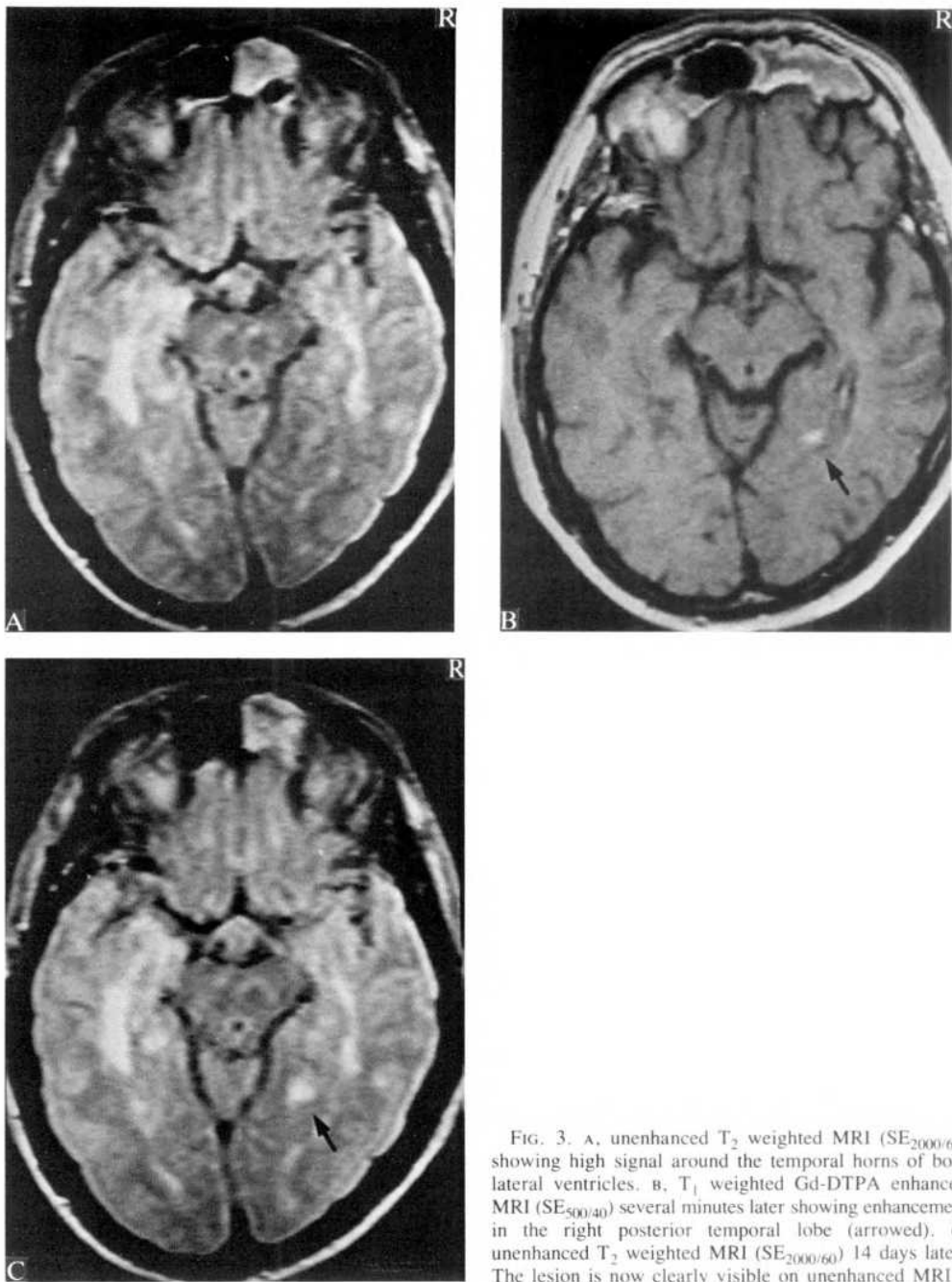


FIG. 3. A, unenhanced T_2 weighted MRI ($SE_{2000/60}$) showing high signal around the temporal horns of both lateral ventricles. B, T_1 weighted Gd-DTPA enhanced MRI ($SE_{500/40}$) several minutes later showing enhancement in the right posterior temporal lobe (arrowed). C, unenhanced T_2 weighted MRI ($SE_{2000/60}$) 14 days later. The lesion is now clearly visible on unenhanced MRI.

of patients when studied appropriately (Lightman *et al.*, 1987; Graham *et al.*, 1989); these appearances are frequently accompanied by leakage on fluorescein angiography. Histologically, the sheathing corresponds with perivenular infiltration with mononuclear

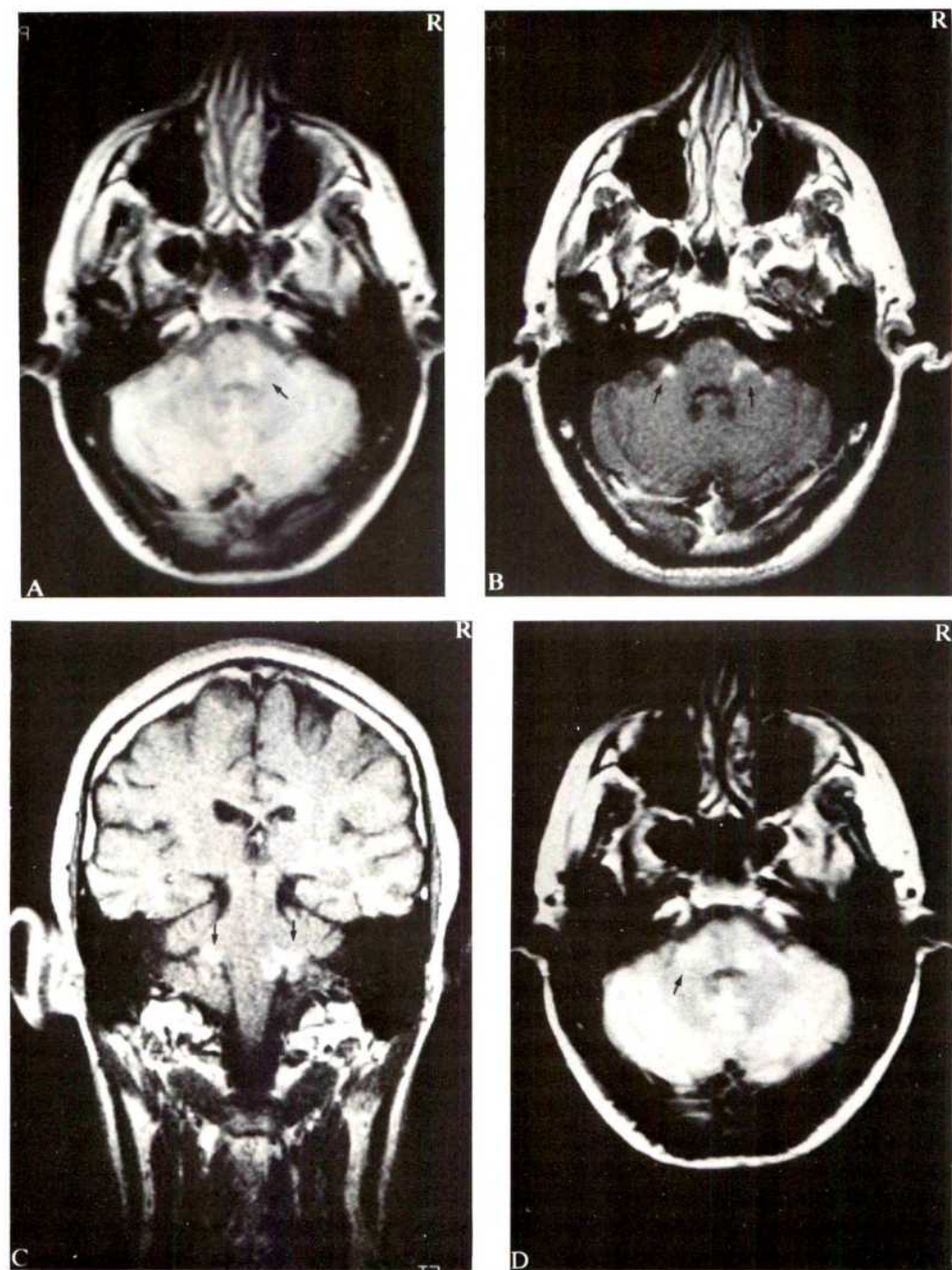


FIG. 4. A, unenhanced T₂ weighted MRI (SE_{2000/40}) showing a lesion in the right pons (arrowed) which extends to the root entry zone of the right acoustic nerve. B, T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) several minutes later showing enhancement (arrowed) in both the right and left root entry zones of the eighth nerve. C, coronal T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) taken immediately after B, also demonstrating the bilateral enhancement (arrowed). D, unenhanced T₂ weighted MRI (SE_{2000/40}) 1 month later which clearly shows a lesion in the left root entry zone.

cells (Fog, 1965) which is in fact quite common in the retina at postmortem (Klintworth, 1982; Arnold *et al.*, 1984) and occurs in the absence of inflammation in the subjacent retinal tissue (Ingrid Allen, personal communication). In summary, the detection of inflammation restricted to blood vessels with normal surrounding tissue suggests that this is a primary event in MS and not a secondary phenomenon.

The clinicopathological paradox

The second question these observations raise is that of the relationship between MRI abnormalities and clinical deficit. Several facts require explanation: MRI lesions are sometimes associated with clinical deficit and sometimes not, and a substantial functional deterioration may occur in the absence of relevant new lesions on MRI.

In order to try to resolve the paradox presented by these dissociations between clinical deficit and pathological activity we must first consider what MRI abnormalities represent. In essence, they indicate the presence of regions in which there are changes in the amount of water and its physicochemical state. In practical terms this comes to changes in intracellular water (i.e., changes in the amount of cytoplasm per unit volume), and in extracellular water (i.e., oedema). The latter has a varying content of protein depending on the type of pathological process present and the stage of its evolution, and will have correspondingly different MRI signals at different times (Barnes *et al.*, 1987a, Larsson *et al.*, 1988). With present clinical MRI technology normal myelin and myelin breakdown products are not directly visualized, though the presence of breakdown products may be suspected (Kermode *et al.*, 1989). Thus the MRI changes chiefly reflect alterations in tissue elements other than the nerve fibres, interference with the function of which is necessary for the development of a clinical deficit. Nevertheless, in CREAE the development of enhancement usually does correspond with areas of myelin damage (Hawkins *et al.*, 1990). A good correlation between MRI abnormality and functional loss is therefore to be expected when lesions occur in regions where there is a concentration of all the nerve fibres essential to a particular function. A good example is provided by Case 4 with deafness and corresponding lesions at the eighth cranial nerve root entry zones, and by optic neuritis where 84% of symptomatic optic nerves show MRI changes (Miller *et al.*, 1988b). Why then are such extensive lesions so often seen in the cerebral hemispheres with little clinical deficit? A number of factors are involved.

In the first place, it must be remembered that many of the most obvious MRI lesions in MS occur in the periventricular regions, damage to which is not currently recognizable by neurological examination though there is an association (but not necessarily a causal connection) with cognitive deficit (Callanan *et al.*, 1989; Rao *et al.*, 1989). Secondly, the possibility of dissociation between nerve fibre damage and oedema has already been mentioned. This is clearly demonstrated in the first case (figs 1A, B, F) in which a very extensive area of abnormal signal corresponded to a smaller zone of enhancement; over the subsequent 2 months the lesion shrank to an area only slightly greater than that of the original area of enhancement. It is difficult to think of a pathological change other than oedema which could resolve so rapidly and completely in 2 months. This interpretation is supported by the biexponential T_2 magnetization decay curves recorded from such areas (D. Barnes, unpublished observations). While it is likely that oedema contributes to physiological and clinical deficit in regions where the tissue is not free

to expand (e.g., the optic nerve in the optic canal; Miller *et al.*, 1988b) the frequent lack of symptoms in patients with extensive oedema, not only in MS but with cerebral tumour, suggests that other factors appearing with a similar time course are more important. Demyelination is one of these, and the products of inflammatory cells might also contribute.

A further complicating factor that will influence the clinical expression of MS lesions is their orientation which is to the veins, which do not necessarily correspond to the direction of nerve fibres. Thus fibres in any particular pathway may traverse some lesions in their long axis, and others at right angles, and others obliquely. The extent of the myelin damage (which ultimately determines the severity of the conduction defects) will be very different in the different orientations. The difficulties are further increased by the fact that lesions are often irregular in outline so that different parts of a pathway at a single level may be damaged to differing extents: a clinical deficit will appear only when conduction in a critical proportion of the fibres is blocked. It must also be remembered that many regions of white matter contain a number of different pathways, so that the extent to which fibres subserving a particular function are damaged will be unpredictable from MRI images.

Finally, in chronic lesions the MRI changes correspond with a persisting increase in tissue water, predominantly extracellular, although gliosis is also present (Barnes *et al.*, 1987a, b). Again, there is not a necessary and direct relationship between these nonneural changes and axonal function which may have been restored to a varying extent by the compensatory process of remyelination or acquisition of the capacity to conduct in persistently demyelinated fibres (McDonald, 1986).

It is now appropriate to consider the explanation of the converse problem: the presence of significant clinical deficit with minimal MRI abnormality. This discrepancy is highlighted by the extensive lesions seen in benign MS when compared with primary progressive MS (Thompson *et al.*, 1989b). An obvious possibility is that many lesions large enough to produce conduction block (paranodal demyelination alone may be sufficient) are beyond the resolution of the present imager. Another possibility is that there is more wallerian-type degeneration in the chronic progressive cases. This process can be initiated by a small focal lesion and the modest gliosis which follows tract degeneration is not likely to change the MRI signal. Finally, especially in MS presenting as progressive spastic paraplegia, it is probable that many of the lesions producing disability are in the spinal cord where imaging is still less satisfactory than in the brain.

With this discussion in mind it is instructive to return to Case 4. Deafness in the right ear was established at presentation, and corresponded with an obvious MRI abnormality in the unenhanced scan at the entry of the eighth nerve to the brainstem. This lesion did enhance, and from animal studies (Hawkins *et al.*, 1990) it is likely that demyelination was present in association with the established and still active inflammation. There was no clinical deficit in the left ear at the time of presentation, though the evoked potential was already abnormal indicating that some nerve fibre damage had taken place; subclinical electrical abnormalities are a commonplace finding in demyelinating disease (Halliday, 1982). A faint area of abnormal signal was present on the unenhanced scan, and there was strong enhancement with gadolinium-DTPA indicating that blood-brain barrier was defective. We interpret these observations as indicating that inflammation was present, producing a small amount of oedema (compatible with the unenhanced images) but that

demyelination was still limited. Two weeks later there was a marked abnormality on the unenhanced scan which still enhanced strongly, making it likely (from experimental studies) that there would be more extensive demyelination, accounting for the deafness which was now present.

In summary, far from being surprised by the variable relationship between the numbers and extent of MRI abnormalities and clinical features, we should expect them. The occurrence of a breakdown in the blood-brain barrier before other MRI evidence of a lesion, or before the development of symptoms in an appropriately sited lesion, provides strong evidence that this vascular change is a very early event in the development of the new lesion.

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INNERVATION TERRITORIES FOR TOUCH AND PAIN AFFERENTS OF SINGLE FASCICLES OF THE HUMAN ULNAR NERVE

MAPPING THROUGH INTRANEURAL MICRORECORDING AND MICROSTIMULATION

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SUMMARY

The peripheral distribution of the fibre content of individual ulnar nerve fascicles supplying skin and muscles of the hand in human volunteers was indirectly mapped by tracing the fields of projected sensation evoked by intraneural electrical microstimulation (INMS) and by tracing receptive fields delineated through intraneural recording of afferent impulse activity elicited by natural stimulation of end organs. Moderate intensity suprathreshold INMS, delivered in cutaneous fascicles, induced nonpainful sensations projecting to stereotyped and coherent areas of skin, the fascicular projected fields (FPFs). Fascicular receptive fields (FRFs) were mapped during microneurographic recording by determining the area of skin which, when activated by light tactile stimuli, elicited afferent neural discharges recorded intraneurally. It was found that at a given electrode position in a skin nerve fascicle, moderate intensity INMS induced nonpainful sensations projecting to a cutaneous field (FPF) that coincides with the FRF, while high intensity INMS induced painful sensations projecting within the cutaneous field of nonpainful sensations. Pain induced by INMS in muscle nerve fascicles was projected to the muscles innervated by that fascicle and, in most instances, to areas beyond the muscular receptive field. The study demonstrates that individual ulnar nerve fascicles, at wrist level, subserve well-defined cutaneous territories in the hand, and that the area of skin covered by the sum of all ulnar fascicular receptive or projected fields matches the maximal possible cutaneous distribution of the ulnar nerve. Insights of practical relevance regarding clinical expression of fascicular nerve injuries are also brought up by this study.

INTRODUCTION

The classical studies of Sunderland (1945) demonstrated that, while at any given level peripheral nerve trunks are subdivided into well-defined fascicles, these anatomical subunits may fuse with each other or may branch along their course. Although Sunderland did not pursue microscopic examination of the topological fate of nerve fibres within nerve fascicles along nerve trunks, it seemed implicit that the fibre content of any one proximal nerve fascicle would become disseminated throughout the innervation territory for the whole nerve. Keeping in mind the existence of such plexuses, Sunderland (1945) questioned 'the possibility of groups of fibres being confined throughout their course to a particular funiculus'. In conformity with this idea, it is often believed that nerve

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injuries selectively affecting single nerve fascicles at proximal level may pass unnoticed because the fibre contents of individual fascicles would not project to compact skin provinces. Nevertheless, more recently, striking compartmentalization of innervation territories has been demonstrated for single fascicles of the human median nerve supplying the skin of the hand (Schady *et al.*, 1983). The methodology in that study involved intrafascicular electrical stimulation by means of Vallbo-Hagbarth microelectrodes evoking sensations localized to coherent cutaneous provinces. The territories thus defined through projected sensation by Schady *et al.* corresponded to receptive fields for individual nerve fascicles which, in turn, had previously been mapped through objective microrecording of afferent activity by Hagbarth *et al.* (1970).

In the present study, we have applied the same methodology as Schady *et al.* (1983) to identify the fascicular territories for cutaneous and muscle fascicles of the human ulnar nerve. In agreement with findings from the human median nerve, we find that ulnar nerve fascicles project to well-defined stereotyped cutaneous provinces of the skin of the hand. In addition, local and remotely referred areas of *pain* evoked by intraneural stimulation of ulnar nerve fascicles supplying muscle are identified in the present report. They are found to be analogous to those described for the median nerve by Torebjörk *et al.* (1984). Together with anatomical clarification, the present study carries clinical relevance in that it highlights remote referral of neuropathic pain emanating from muscle fascicles of the ulnar nerve, and suggests that proximal partial nerve lesions involving single fascicles may masquerade as terminal branch neuropathies.

MATERIAL AND METHODS

Subjects and experimental procedure

Sixty-six experiments were performed on 16 healthy adults (7 females aged 20, 25, 26, 28, 30 and 32 yrs, and 9 males aged 22, 24, 28, 30, 32, 33, 36, 49, 55 yrs) and 11 patients (5 females aged 29, 32, 45, 56 and 60 yrs, and 6 males aged 26, 28, 29, 32, 36, 60 yrs) affected by neurological diseases not involving the tested ulnar nerve or central nervous system functions. All 27 volunteers gave informed consent before entering the study; 59 experiments were performed at wrist level and 7 at elbow level. The experimental subject either reclined supine on a bed for elbow recordings, or sat in a reclining armchair with the arm comfortably supported for wrist recordings. Recording and reference electrodes were inserted through the intact skin overlying the right or left ulnar nerve at the wrist (1–5 cm proximal to the pisiform bone) or at the elbow (6–15 cm proximal to the ulnar groove). Interelectrode distance was ± 1 cm.

After insertion, the recording electrode was advanced in the direction of the nerve while passing electrical pulses through the electrode until the subject reported cutaneous paraesthesiae projected to the hand, or until muscle contraction was observed. These phenomena confirmed intraneural location of the electrode. Parameters for intrafascicular stimulation during electrode positioning were square wave pulses with a duration of 250 μ s, an amplitude of 0.6 V and frequency of 20 Hz. Once the electrode settled in a stable intrafascicular position, that is, the subject reported consistent sensations at low thresholds (usually below 0.3 V), the stimulus amplitude was reduced to zero and then gradually increased. Intrafascicular stimulation parameters during mapping of fascicular projective fields (FPFs) consisted of pulses of 250–400 μ s duration and 0.1–15 V amplitude, which corresponds to currents up to 500 μ A assuming an electrode impedance of 30–100 k Ω (Vallbo and Hagbarth, 1968). For mapping of FPFs, subjects were asked to describe the subjective quality and to draw the location of sensations induced by intraneural microstimulation (INMS) on a real size xerographic copy of their hand (fig. 1).

After the fascicular territory of projected sensation (FPF) evoked by INMS was mapped, the system was changed to a recording mode by a switch on the preamplifier connecting the electrodes to an amplifier, oscilloscope and loudspeaker, thus permitting audiovisual monitoring of neural discharges. Once in recording mode, the fascicular receptive field (FRF) was identified by gently stroking the skin with a wooden stick,

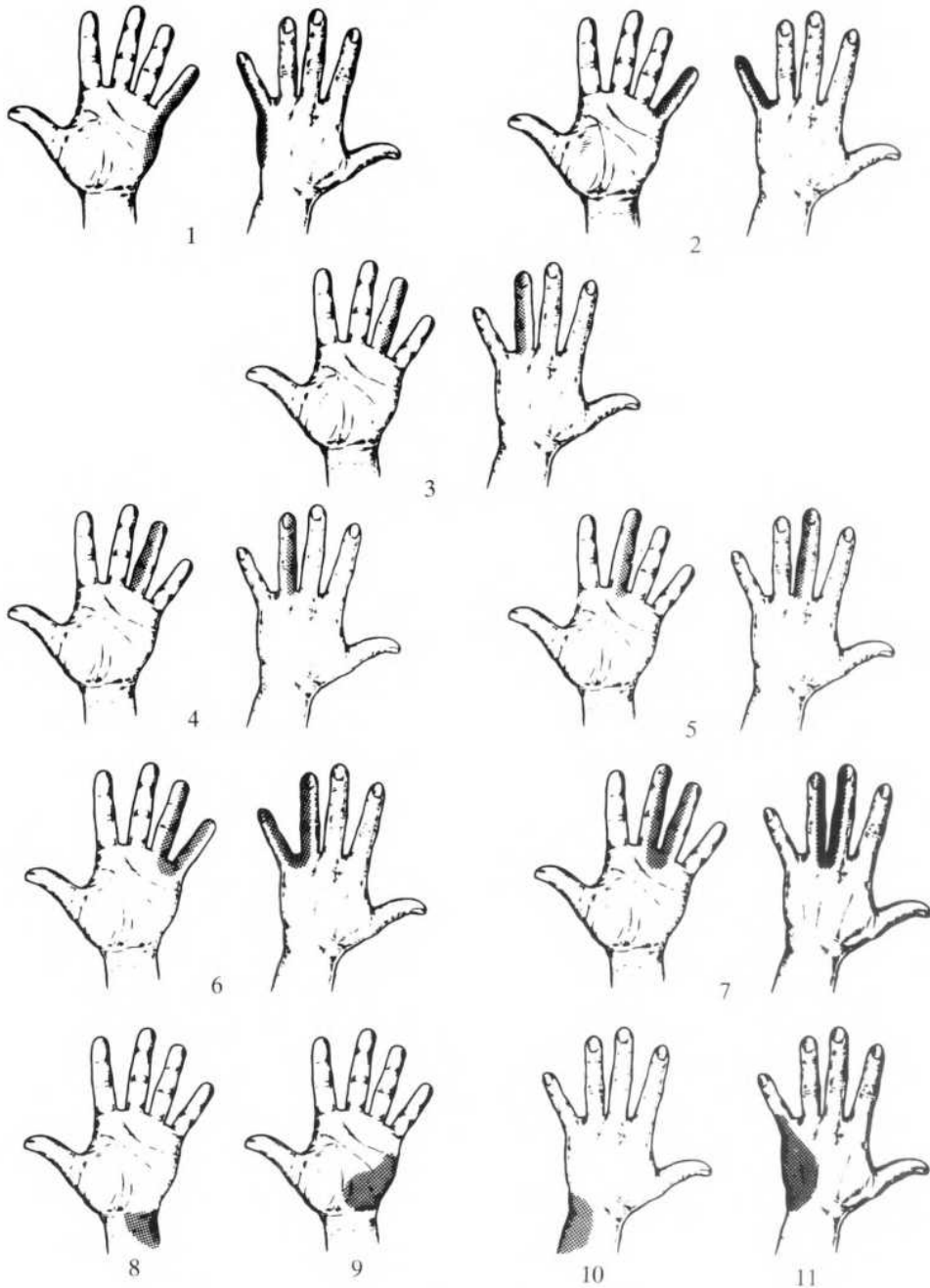


FIG. 1. Fascicular projected fields: areas of the hand where nonpainful sensations are projected during intraneural stimulation of moderate intensity at wrist level of single ulnar nerve fascicles supplying skin. These areas match fascicular receptive fields. The first 7 pairs of profiles (1-7) represent 7 fascicular territories viewed from palm or dorsum. The profiles in wrist or hand exclusive of fingers (8-11) represent 4 different fascicular territories, each projecting to only one aspect of the hand. This yields a total of 11 possible fascicular territories for the population examined (27 subjects and 58 skin nerve fascicles).

a brush or a finger. Borders of the cutaneous territory were defined using nonpainful pressure with a von Frey hair (log 5.88 = 76 g). Care was taken to avoid vibrating stimuli to minimize activation of sensitive, low threshold mechanoreceptors (Pacini units) at a distance from their anatomical receptor. The identified cutaneous territories (FRFs) were then cross-hatched on the skin with a pen. Colour photographs of the hand were made using a Polaroid camera.

If a fascicle innervating muscle was identified, careful scrutiny of the muscles supplied by that fascicle was performed by observing muscle twitching induced by INMS and by mapping sources of afferent discharges recorded intraneurally from muscle receptors in response to light mechanical stimulation of muscles or tendons.

Instrumentation

Microelectrodes used for intraneural stimulation and intraneural recording were made of tungsten with a 50–180 μm tip length and 5–15 μm tip diameter, as recommended by Vallbo and Hagbarth (1968). Electrical stimulation was delivered from a Grass S48 constant voltage apparatus. Recorded signals were displayed on a Tektronix 5113 oscilloscope for real time monitoring, and stored on a Gould 6500 tape recorder for further analysis.

RESULTS

Projected and receptive fields of skin fascicles for nonpainful sensations

A total of 58 cutaneous fascicles was studied. Eleven different cutaneous fascicular receptive fields were identified from the material. Cutaneous FRFs matched FPFs mapped using nonpainful electrical stimulation (fig. 1). In the few cases where agreement between FPFs and FRFs was not complete, receptive fields were generally larger than the corresponding projected fields, the difference being no more than 4 mm. Each pattern was replicated in more than 1 subject, with the exception of pattern 5. Incidence of individual territories shown in fig. 1 was pattern (P) P1 = 13, P2 = 6, P3 = 10, P4 = 3, P5 = 1, P6 = 8, P7 = 3, P8 = 5, P9 = 3, P10 = 4, and P11 = 2. The skin field supplied by an individual fascicle was often equivalent to that supplied by a digital nerve, that is, it covered the lateral or the medial half of one finger, or two contiguous halves of adjacent fingers (the interdigital web), or an oval shaped area of skin on the ulnar aspect of the palm or hand dorsum. The FPFs and the FRFs were essentially identical in their spatial characteristics for experiments at wrist level as compared with those at elbow level. Combining all cutaneous receptive or projected fields determined the maximal ulnar cutaneous territory. It extended to the midline of the middle finger on dorsal and palmar aspects of the hand (fig. 2).

Fascicles innervating skin outside the usual nerve territory were identified in 5 of the 27 subjects (19%). These supplied the lateral aspect of the fourth finger (3 subjects), the medial side of the third finger (1 subject), or the web between the third and fourth fingers (1 of the former subjects and 1 additional subject). Thus the present material shows that extension of the ulnar nerve territory beyond the midline of the fourth finger is not uncommon, as it occurred in almost one-fifth of the volunteers in this series. Such cutaneous distribution of ulnar nerve fibres is occasionally reported (Haymaker and Woodhall, 1953). It should be kept in mind that the total ulnar nerve territory displayed in fig. 2 is a composite derived from superimposition of fascicular territories determined in many different individuals. In no case was it possible to collect all the complementary fascicular territories in any given individual. It is therefore not surprising that small islands of uncharted skin might be detectable in this kind of study.

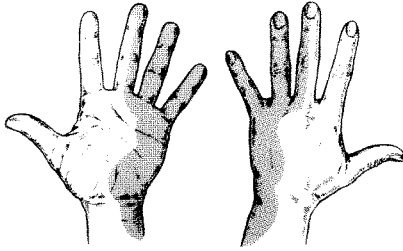


FIG. 2. Composite profile of skin territory of ulnar nerve, derived from superimposition of individual ulnar fascicular territories, as shown in fig. 1.

Projected fields and receptive fields of muscle nerve fascicles for nonpainful sensations

Intraneural stimulation of 8 fascicles innervating muscle produced observable muscle contraction in two patterns: flexion and abduction of the fifth finger, or flexion alone of the fourth and fifth fingers at the metacarpophalangeal joint. Receptive fields of muscle nerve fascicles were determined by applying repetitive deep pressure to the hand to elicit discharge of muscle and tendon afferents. Muscle receptive fields were limited either to the hypothenar eminence or to the central part of the hand in the metacarpal region. Four mixed fascicles supplying both skin and muscle were found. Two fascicles predominantly innervating hypothenar muscles had small cutaneous components at the wrist (fig. 1, no. 8). The other 2 mixed fascicles also supplied hypothenar muscles but had larger cutaneous components, about the size of an average fascicular territory (fig. 1, no. 1).

Sensations of pulling and joint movement during INMS of muscle nerve fascicles are presumed to be due to indirect activation of skin receptors as a consequence of skin movement induced by muscle contraction, as it was also possible to activate muscles without any cognitive sensation.

Projected fields of pain for muscle and skin nerve fascicles

Stimulating skin fascicles at wrist level with suprathreshold painful current intensities always produced pain referred to the hand. It was described as a burning, crushing, or pressing sensation. Pain was felt either superficially in skin, or deep in the hand. Areas of early painful sensation in skin were localized to spots of variable size, 0.5–3 cm in diameter. These small areas of superficially projected pain were always within the territory of projected nonpainful sensation (FPFs). Subjects localized deep pain to joints, tendons or bones in the hand. Deep pain was also always projected within the nonpainful fascicular cutaneous territory (fig. 3).

Increasing intensity of the electrical stimulus still further resulted in enlargement of the painful areas, which coalesced at submaximal stimulus intensity (20 V, 400 μ s duration). Greater intensity was not tolerated; it produced unbearable pain and autonomic reactions. The largest painful FPFs for cutaneous fascicles were still within the territory of projected nonpainful sensation, suggesting that cutaneous fascicular territories for small calibre afferent fibres are congruous with those for large myelinated fibres.

Pain induced by electrical stimulation of ulnar muscle nerve fascicles at wrist level was often projected to the same muscle or group of muscles innervated by the stimulated nerve fascicle, in which case projected and receptive fields were grossly congruent.

However, pain also projected beyond the fascicular territory in 75% of the trials (6/8). These remote painful sensations projected to the forearm, arm, scapular region and chest (fig. 4).

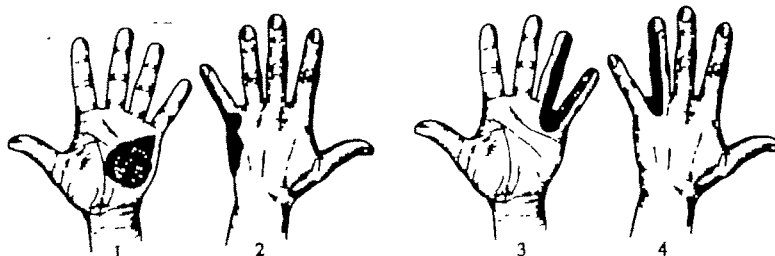


FIG. 3. Areas of the hand where painful sensations are projected during strong intraneural stimulation of single ulnar nerve fascicles supplying skin. As in fig. 1, profile 1 projects to palm only and profiles 2, 3 and 4, involving fingers, project to both palmar and dorsal aspects (only one aspect is shown for each). Dark area represents projection of maximal pain.

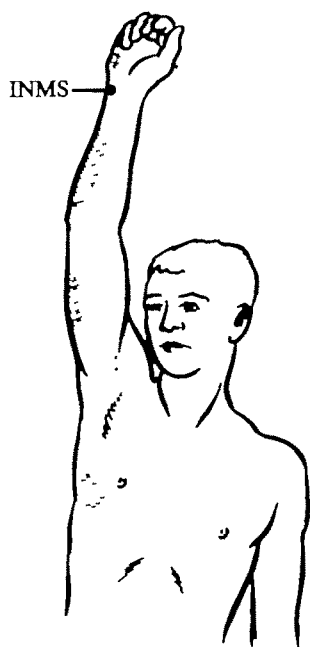


FIG. 4. Areas of the body where painful sensations may be referred during strong intraneural stimulation at wrist level of single ulnar nerve fascicles supplying hand muscles. Muscle pain was projected most commonly to distal muscles in the hand. Proximally referred pain was localized most commonly to ulnar forearm and less frequently to posterior upper arm, lateral chest wall and scapular region (not shown). INMS = intraneural muscle fascicle stimulation.

DISCUSSION

Authentication of the method

While it is conceivable that the compartmentalized cutaneous territories for human ulnar nerve fascicles, as defined in the present study, might be a psychophysical artefact, there is support for their veracity. The territories of projected sensation evoked by

intrafascicular stimulation match the territories of receptive fields objectively delineated, from which natural stimulation of cutaneous receptors evokes afferent activity recorded from the same fascicles. This finding has been reported previously for the median nerve (Schady *et al.*, 1983). It stands against the criticism raised by Wall and McMahon (1985), claiming that the fascicular compartments reported for the human median nerve by Ochoa and Torebjörk (1983) were 'abstracts by the brain'. Wall and McMahon stated 'If a high intensity intraneuronal stimulus is applied to a fasciculus in the median nerve, the subject experiences a precise area of sensation in a fraction of the median nerve territory (ref). It is known anatomically that such a fascicle contains fibres from all areas supplied by the median nerves (refs). This means that the psychological experience is generated by a mechanism which selects certain afferent information and ignores impulses in fibres which originate from other areas of skin' (Wall and McMahon, 1985). Schady *et al.* (1983) argued against the concept that 'a fascicle contains fibres from all areas supplied by the nerve'. The misconception is based on overinterpretation of Sunderland's (1945) evidence for gross anatomical intermingling of nerve fascicles.

Neuroanatomy

The results presented here for the human ulnar nerve supplement those reported by Schady *et al.* (1983) for the median nerve, and provide additional knowledge of normal human neuroanatomy. Compartmentalization of fascicular innervation territories of the skin of the human hand is not confined to distal portions of nerves. Indeed, both for the median and ulnar nerves, compartmentalization prevails in the upper arm. Further, there is anecdotal evidence which suggests that it may prevail even at root level. Fig. 307 of Foerster (1929, p. 1380) illustrates a very well-defined province of cutaneous sensory loss following traumatic lesion of a cervical root, which is equivalent to a median nerve fascicular compartment as described by Schady *et al.* (1983).

Projected fields for pain evoked by excitation of skin nerve fascicles in human ulnar nerve

One aspect of this study that was not approached by Schady *et al.* (1983) for the human median nerve deals with the fascicular projection territories of *pain*, as opposed to the projection territories of nonpainful sensations. The finding that painful cutaneous fascicular ulnar projections are contained within the perimeter of the projection of nonpainful sensations does not necessarily mean that the complete fascicular territories for both types of projections are identical. This issue could not be resolved because pain experienced by the volunteer often prevented the use of stimulus intensities adequate for complete saturation of the painful fascicular projection.

The present findings suggest that the fascicular population of nerve fibres concerned with transmission of cutaneous pain projects to well-defined districts within the total cutaneous innervation territory of the human ulnar nerve. Such areas closely match the innervation territory of nonnociceptor mechanoreceptor afferents contained in the same fascicle.

Muscle pain

Pain was the only primary sensation induced by stimulation of ulnar nerve fascicles destined to muscles and, as described for the human median nerve (Torebjörk *et al.*,

1984) it was often projected to areas of the body which are remote, proximally situated and not supplied by the same nerve. Poor localization of painful sensations originating from deep structures, and muscle in particular, is well known since the classical experiments by Kellgren (1938). Surprisingly, the usual explanation of this phenomenon is through the theory of convergence from several afferents to one common cortical representation (Ruch, 1979). As pointed out already (Torebjörk *et al.*, 1984), *divergence* from common peripheral territories to different cortical areas is an alternative, more logical, explanation. If so, that divergence is associated with afferents supplying muscle rather than with those supplying skin, at least with regard to the upper extremities.

Clinical relevance

Several clinical repercussions emanate from the present study. For example, in dismissing clinical sensory abnormalities as psychogenic in origin, the standard idea 'the pattern of deficit does not fit a known anatomical nerve territory' is often presented as an argument. Obviously, individual fascicular territories do not fit the known pattern for any given nerve but, of course, they should not be regarded as hysterical constructs. Admittedly, it is unusual to see patients with well-defined fascicular patterns of sensory deficit in the clinic. This can largely be explained through the infrequent occurrence of severe nerve injuries confined to single fascicles. The possibility of double or multiple fascicular representation for any given area of skin, as suggested by Schady *et al.* (1983), could make those cases even more difficult to detect through examination of sensory deficits. Also, ulnar nerve lesions producing sensory symptoms extending beyond the usual ulnar one-and-one-half fingers should not be regarded as nonanatomical. The data presented here suggest this occurs fairly commonly; it was found in 19% of the volunteers examined in this study.

On the other hand, it should be anticipated that *positive* subjective sensory phenomena derived from single fascicular lesions will be well expressed symptomatically, as paraesthesiae or pain, and yet will not necessarily express a coexistent sensory *deficit*. If the safety factor of multiple fascicular representation is a significant one, then it is likely that fascicular lesions occur more frequently than imagined, and the clinician should be prepared to take seriously positive sensory symptoms localized to fascicular territories in the absence of detectable sensory deficit. Again, since compartmentalization of fascicular cutaneous territories may prevail at proximal levels, even in nerve roots (Foerster, 1929), sensory deficits affecting half a finger or a web should not necessarily be attributed to lesions in digital nerves in hand or fingers.

Further, clinicians should remain alert to the possibility that chronic dull pains projected to shoulder, upper arm, or scapular region, with little else in the way of classical symptoms and signs of ulnar neuropathy, might be due to ectopic impulse activity arising from injury to ulnar nerve fascicles supplying muscle, giving rise to proximally referred pains. We have come across a handful of such cases (unpublished observations). Others have documented a similar situation for irritation of human median nerve in the clinic (Crymble, 1968; Golding, 1968) and in human experiments (Torebjörk *et al.*, 1984).

Routine electrophysiological nerve conduction studies can evaluate conduction deficit but not irritative pathophysiological change. Further, only deficits in large calibre fibres in whole nerve trunks or, at best, in bundles of fascicles, can be detected. Thus normal nerve conduction studies in patients should not be taken as definitive evidence against

an organic basis for discretely localized sensory complaints, either positive or negative. Unfortunately, microneurography and INMS are not routinely available to assist in clarifying puzzling neuropathic clinical problems, such as pure positive sensory phenomena, proximal pains suspected as being referred from entrapped limb nerves, and sensory deficits of unusual distribution. As a substitute, Highet's (1942) approach using local nerve block valuably detects partial nerve injuries, anomalous innervation, and potentially pinpoints a local nerve source of proximally referred pain.

There is striking order in the pattern of fascicular territories for human ulnar and median nerve supplying the skin of the hand. Nevertheless, the present study is based on psychophysical (FPFs) and neurophysiological (FRFs) data obtained in subjects with a normal nervous system, and this situation might be modified in patients with pathological afferent pathways. Studies performed after section of human nerve (Rivers and Head, 1908; Trotter and Davies, 1909; Denny-Brown, 1965) and of monkey roots (Kirk and Denny-Brown, 1970) reported the appearance of hypersensitivity and hyperalgesia in an area surrounding the area of sensory loss. This factor might lead to bizarre patterns of sensory abnormality in patients with fascicular lesions.

ACKNOWLEDGEMENTS

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VOLUME CONDUCTION OF THE PARIETAL N20 POTENTIAL TO THE PREROLANDIC FRONTAL AREA

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SUMMARY

Somatosensory evoked potentials were recorded from the frontal and parietal areas in patients with various lesions in the central nervous system on stimulation of the median nerve. Five representative cases who showed a selective loss of the positive potential from the frontal area are reported. In each case, the parietal N20 potential was relatively well preserved, and the midposition between the frontal and central areas (FC area) showed a negative potential following P14. The peak of this negative potential was synchronous with that of the parietal N20 potential. This negativity on the FC area is considered to be a volume conducted potential from the parietal N20 to the prerolandic frontal area. Such an anterior volume conduction of the parietal N20 would not be explained by the concept of a tangentially oriented dipole generated in the posterior bank of the central sulcus. Instead, for the generator of the parietal N20 potential, a radically oriented dipole generated mainly in the parietal area is postulated.

INTRODUCTION

Recent studies of somatosensory evoked potentials (SEPs) on stimulation of the median nerve or median-innervated fingers revealed that evoked responses were recorded from the frontal as well as the parietal area (Broughton, 1969; Desmedt and Cheron, 1980, 1981; Lueders *et al.*, 1983; Mauguière *et al.*, 1983; Yamada *et al.*, 1984, 1985; Desmedt and Bourguet, 1985; Kakigi, 1986; Tsuji and Murai, 1986; Deiber *et al.*, 1986; Desmedt *et al.*, 1987; Dinner *et al.*, 1987; Tsuji *et al.*, 1988). Broughton suggested that the frontal components (P22 and N30) were the mirror images of the parietal N20 and P27 potentials which might be generated in the posterior bank of the central sulcus (Broughton, 1969). On the other hand, Mauguière *et al.* (1983) reported the dissociated loss of frontal and parietal components of SEPs and suggested that the early frontal components (P22 and N30) of the SEPs recorded from the frontal area contralateral to the stimulation were related to generators in the frontal cortex on that side and could not be referred to simple mirror images (phase reversal) of the parietal responses. Furthermore, Deiber *et al.* (1986) and Desmedt *et al.* (1987) suggested that the frontal positive potential might be composed of two components, one being a prerolandic P22 (a central P22 in the

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nomenclature of Deiber *et al.*) generated in the prerolandic frontal cortex and the other a frontal P20 which might be a mirror image of the parietal N20 (Deiber *et al.*, 1986; Desmedt *et al.*, 1987). In their interpretation, there should be two dipoles. That for the prerolandic P22 is radially oriented and may be generated in the frontal cortex, and the other for the frontal P20 and parietal N20 is tangentially oriented and may be generated in the posterior bank of the central sulcus (*see* fig. 13 in Desmedt *et al.* 1987).

We recorded SEPs from the frontal and parietal areas after median nerve stimulation in patients with various lesions in the central nervous system. In this study, the dissociated loss of the frontal and parietal responses was noted as already reported by Mauguière *et al.* (1983). In addition, we found a negative potential following P14 in the prerolandic frontal area, the peak of which was synchronous with that of the parietal N20 in the patients who showed a selective loss of the frontal positive potential. This negativity is considered to be a volume conducted potential of the parietal N20 to the prerolandic frontal area. It seems difficult to explain such a volume conduction of the parietal N20 potential to the prerolandic area in terms of a tangentially oriented dipole generated in the posterior bank of the central sulcus, as suggested by Deiber *et al.* (1986) and Desmedt *et al.* (1987). In this report, we describe 5 cases who showed volume conduction of the parietal N20 potential to the prerolandic frontal area.

MATERIAL AND METHODS

SEPs were recorded in 92 patients with various lesions in the central nervous system, aged 15–72 yrs. CT scans or MR images were available for all the patients. The recordings were made with silver disc electrodes placed in accordance with 10–20 International system (Jasper, 1958) with some selections of F3, F4, C3, C4, P3 and P4. Additional placements such as FC3, FC4, CP3 and CP4 were also employed in about one-third of the subjects. FC3 represents the midposition between F3 and C3, CP3 between C3 and P3, and so for FC4 and CP4. The linked earlobes served as a reference electrode in all subjects and an electrode impedance was maintained below 5 k Ω . The SEPs were recorded while the subjects lay supine in a semidarkened, air-conditioned room. They were instructed to relax with eyes closed, but not to fall asleep. No sedative medication was given. The EEG was monitored throughout the recording session on most occasions. Electrical activity from the recording electrodes was amplified by differential a.c. amplifiers with bandpass of 5–3000 Hz (–3 dB). An analysis time of 40–50 ms was used with 512 points per channel, and 700 to 1000 samples were taken for averaging (NEC San-ei 7T17). The potentials from 8 to 10 channels were simultaneously recorded in all subjects with an automatic rejection unit for artifactual activity. When the EEG monitoring showed massive contaminations of EMG activity, the summation was also rejected by examiners. The recordings were performed by stimulating successively either the right or the left side and at least twice on either side in order to verify the reproducibility of the recorded potentials. The stimulating electrodes were a pair of silver electrodes, which were attached to the skin overlying the median nerve just proximal to the wrist with the cathode about 2 cm proximal to the anode. Stimuli to the median nerve were delivered with a pulse duration of 0.2 ms through a stimulus isolation unit at a rate of 2–4 Hz. The stimulation was adjusted to evoke modest twitches of the thumb.

In this report, the peaks will be labelled as P14, frontal P22, frontal N30, parietal N20 and parietal P27, irrespective of the actual peak latencies (Donchin *et al.*, 1977; Desmedt, 1984).

RESULTS

Five representative cases will be described as below. All showed a selective loss of the frontal positive potential with a fairly well preserved parietal N20 potential. Case 1, a woman aged 65 yrs, had a haematoma in the right putaminal region with some extension to the posterior limb of the internal capsule. She showed mild left-sided weakness without

discernible sensory impairment on the day of SEP recording approximately 1 month after the haemorrhagic insult. The upper part of fig. 1 shows SEPs on both sides after left median nerve stimulation, and the lower part after right median nerve stimulation. Fig. 2 shows the same results as in fig. 1, but demonstrates the responses contralateral to the stimulation at a magnified scale. After stimulation of the left median nerve, a

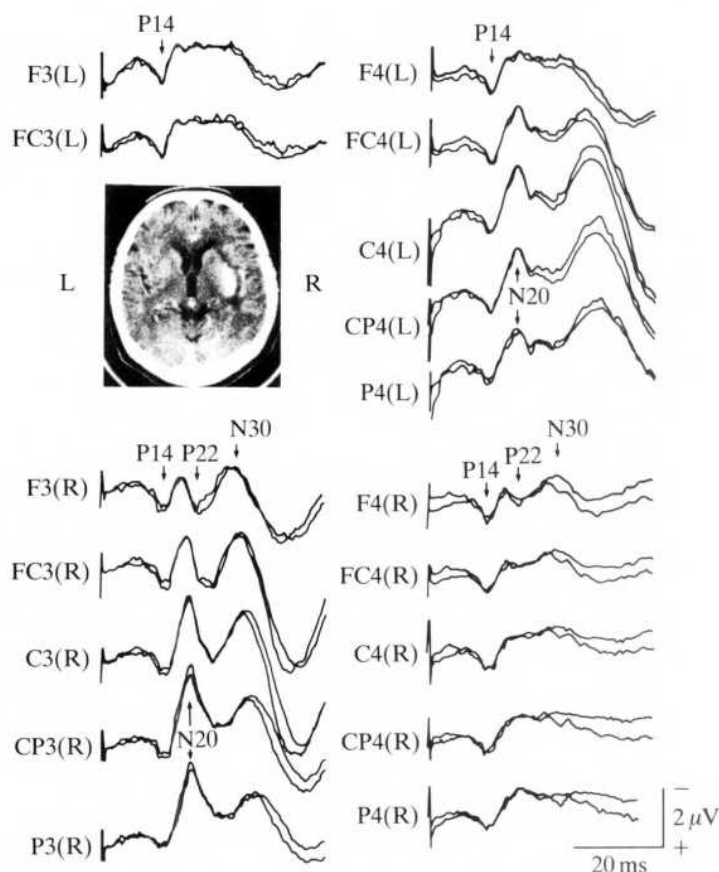


FIG. 1. *Case 1*, a 65-yr-old woman with a right putaminal haemorrhage. The upper part shows SEPs on both sides after left median nerve stimulation, and the lower part after right median nerve stimulation. (L) and (R) indicate the left-sided and right-sided stimulations, respectively. FC3 represents the midposition between F3 and C3, CP3 between C3 and P3, and so for FC4 and CP4. Note the absence of the frontal positivity after stimulation of the left median nerve. Voltage calibration is applicable to all traces, upward being negative. Time scale is for all records.

well defined N20 potential was recorded from the contralateral parietal region without discernible frontal P22 and N30 components on both sides, as shown in the upper part of fig. 1. Well defined negative peaks following P14 were also recorded from the C4 and FC4 areas. The peak latencies of these negative potentials were the same as those of the parietal N20 potentials on CP4 and P4 areas, and their waveforms were very similar to those of the parietal N20s, as shown in the right column of fig. 2. As the FC4 area is considered to be located in the prerolandic frontal area (Jasper, 1958), this

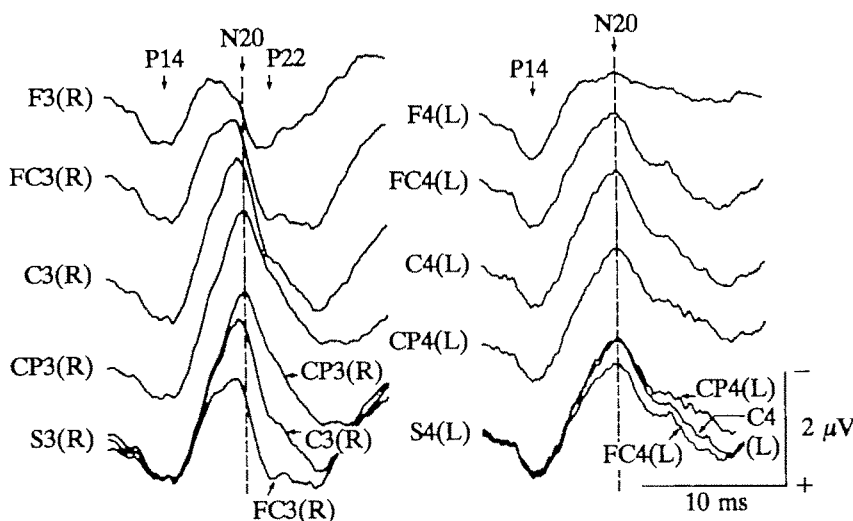


FIG. 2. *Case 1* Contralateral responses after stimulation of the median nerve on either side. The time and amplitude scales are magnified. S3(R) represents the superimposed traces of the activity on the FC3(R), C3(R) and CP3(R) areas. The same was done for S4(L).

result would indicate that the volume conducted potential of the parietal N20 could be recorded from the prerolandic frontal area with some reduction in amplitude when the frontal positive potential was absent. With stimulation on the right side, the normal responses were obtained as shown in the lower part of fig. 1 and the left column of fig. 2. The FC3 area showed a negative peak following P14, but its amplitude was much reduced and its peak latency was slightly earlier as compared with the parietal N20 potentials recorded from P3 and CP3 areas, as shown in figs 1 and 2.

Similar results were obtained from 4 other patients in the stable stage after the acute event as shown in fig. 3. Fig. 3A shows the results obtained from a 66-yr-old woman with a right putaminal haemorrhage (Case 2). Fig. 3B shows the recordings from a 67-yr-old man with a small left thalamic infarct (Case 3). In fig. 3C and D are shown the results taken from a man aged 45 yrs with a small deep cerebral white matter infarct on the left (Case 4) and from a 26-yr-old woman with a white matter infarct in the left frontal area (Case 5), respectively. Their MR images are shown in the lowest part of the figure. In this figure, the thicker traces represent the recordings from the affected hemisphere after median nerve stimulation on the hemiparetic side. The thinner traces represent those from the unaffected hemisphere after stimulation on the nonhemiparetic side. As shown in the figure, the frontal positive potentials were virtually absent while the parietal N20 potentials were fairly well preserved after stimulation on the hemiparetic side. The negative potentials following P14 were clearly seen in the FC area with the peak latencies synchronous with those of the parietal N20 potentials as indicated by the broken lines.

DISCUSSION

In all the 5 cases, there were selective losses of the positive potentials in the frontal region with fairly well preserved parietal N20 potentials recorded from the affected

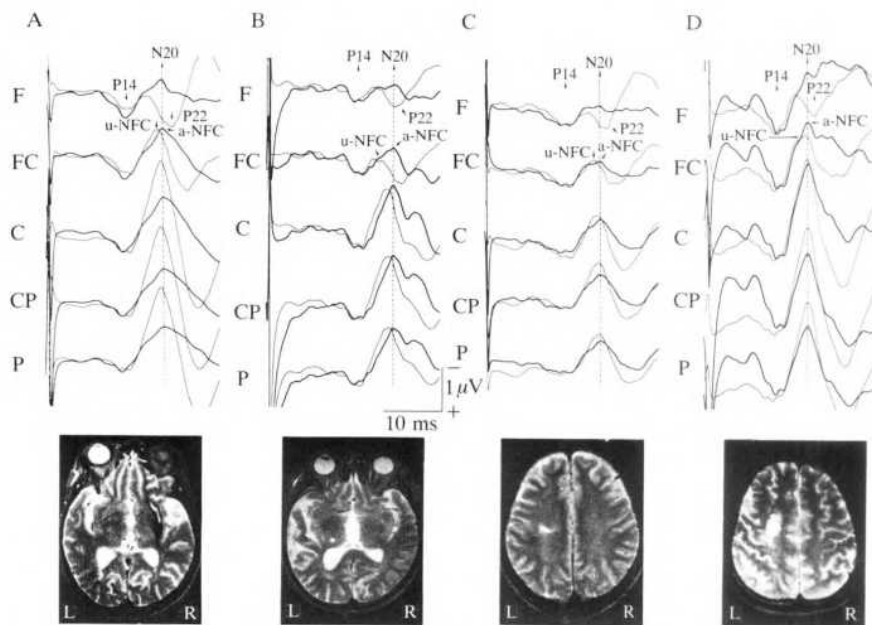


FIG. 3. Recordings from 4 other subjects. The heavy traces represent the recordings from the affected hemisphere with stimulation on the hemiparetic side. The thin traces represent those from the unaffected hemisphere with stimulation on the nonhemiparetic side. Two traces are superimposed. An a-NFC represents the negativity following P14 on the FC area over the affected hemisphere after stimulating on the hemiparetic side, and a u-NFC represents one over the unaffected hemisphere after stimulating on the nonhemiparetic side. Note the peak of a-NFC potential synchronous with that of the parietal N20.

hemisphere after stimulation on the hemiparetic side. In addition, the negative potentials following P14 were recorded from the prerolandic frontal area, notably the FC area. The peak latencies of these negative potentials almost coincided in time with those of the parietal N20 potentials. On the other hand, the FC area on the unaffected hemisphere after stimulation on the nonhemiparetic side showed the negative deflections following P14, the amplitudes of which were considerably smaller and the peak latencies of which were slightly earlier than those of the parietal N20 potentials.

For convenience, we label the negative potential following P14 recorded from the FC area on the affected hemisphere after stimulation on the hemiparetic side as the affected NFC potential or a-NFC. The negative potential following P14 recorded from the FC area on the unaffected hemisphere after stimulation on the nonhemiparetic side will be labelled as the unaffected NFC potential or u-NFC.

These results indicate that the a-NFC may have represented passive volume conduction of the parietal N20 potential. This volume conduction of the parietal N20 potential is considered to have become manifest because of the selective absence of the positive potential in the frontal area. How purely the a-NFC represents a volume conducted potential of the parietal N20 would depend on the completeness of the selective loss of the positive potential in the frontal area. On the other hand, the u-NFC is considered to be an admixture of the positive potential in the frontal area and the volume conducted

potential of the parietal N20 potential. Therefore, the u-NFC can be small and actually not negative to the baseline in some cases, as shown in Case 3. In addition, the peak latency of the u-NFC is considered to be slightly earlier than that of the parietal N20 potential because of the summation of the positive potential with a slightly later peak latency (P22).

This interpretation is partly supported by the findings shown in fig. 4. In FC-F row of fig. 4, the digital subtractions of the potentials on F area from those on FC area (FC-F) are demonstrated. All potentials shown in fig. 4 were recorded from the unaffected hemisphere with stimulation on the nonhemiparetic side in Cases 1 (A), 2 (B) and 3 (C). Digital subtraction (FC-F) revealed the negative peak to be synchronous with the parietal N20 in each case, as indicated by N20' in the figure. If the u-NFC consists of the admixture of frontal P22 and the volume conducted potential of the parietal N20, u-NFC minus frontal P22 would leave the volume conducted potential of the N20 on the FC area, the peak latency of which should be synchronous with that of the parietal N20. This was the case as shown by the broken lines in fig. 4.

Such a volume conduction of the parietal N20 to the prerolandic frontal (FC) area is difficult to explain by the concept of a tangentially oriented dipole generated in the posterior bank of the central sulcus. The tangentially oriented dipole has been proposed to be a surface positive-depth negative potential in the cortex of the posterior bank of the central sulcus (Broughton, 1969; Lueders *et al.*, 1983; Desmedt *et al.*, 1987). This tangential dipole must have a zero potential within the cortex at the site of the posterior bank. Such a tangential dipole is considered to produce a zero potential around the central area which is nearly at right angles to the axis of the tangential dipole, a positive potential

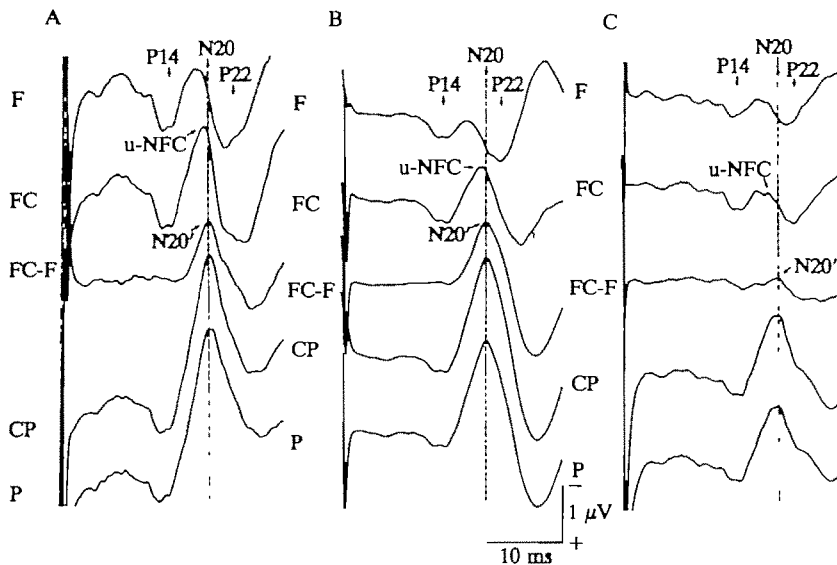


FIG. 4. Digital subtractions of the potential in the F area from that in the FC area (FC-F) are shown in the FC-F row. Column A shows the recordings from Case 1, B from Case 2, and C from Case 3. N20's are the negative potentials as revealed by the subtractions. See text for details.

in the prerolandic area and a negative potential in the postrolandic area, in spite of some variations in the direction or in the shape of the central sulcus (*see* fig. 5A, C). With this dipole theory, the negative potential should not appear in the frontal area. However, we recorded negative peaks from the frontal area which were synchronous with those of the parietal N20.

It was recently suggested that the frontal positivity might be composed of the prerolandic frontal P22 (a central P22 in the nomenclature of Deiber *et al.*) generated in the frontal cortex and of the frontal P20 which might be a mirror image of the parietal N20 (Deiber *et al.*, 1986; Desmedt *et al.*, 1987). According to this theory, the frontal P20 should be recorded in the cases that showed the selective loss of the prerolandic P22 with the parietal N20 preserved (*see* fig. 5c). However, in our cases in which the frontal P22 was virtually absent, while the parietal N20 was apparent, the discernible frontal positive peak synchronous with the peak of the parietal N20 was not observed. There were small negative deflections in the frontal area (F area in the figures), rather than the 'frontal P20' after stimulation of the hemiparetic side, as shown in figs 1, 2 and 3.

In this context, we postulate a radially oriented dipole in the parietal cortex contralateral to the stimulation as the generator of the parietal N20 potential, and that in the frontal area contralateral to the stimulation as the generator of the frontal P22 potential recorded from the contralateral side. This radial dipole in the parietal area should be a surface negative-depth positive potential as shown in fig. 5B. This type of dipole is considered to be mediated by the superficial thalamocortical pathway as proposed by Sasaki *et al.* with the results obtained by studies of recruiting and augmenting responses (Sasaki *et al.*, 1970; Sasaki, 1976/1977). The primary somatosensory evoked response was reported to be a surface positive-depth negative potential in cat experiments (Matsuda *et al.*, 1972). Their study seems to indicate the absence of the superficial thalamocortical pathway to the primary somatosensory cortex. On the other hand, it was shown that the surface negative-depth positive potential could be elicited in the primary somatosensory cortex

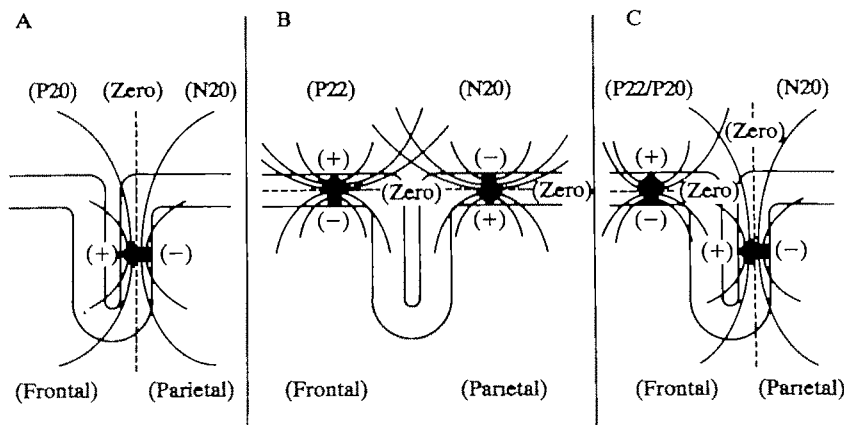


FIG. 5 Three models for the generators of the positive potential in the frontal area and the parietal N20 potential. The central sulcus is drawn along with the frontal and parietal cortices. Our view is shown in the middle part (B) of the figure

of monkeys, which was revealed by the recording of the premovement cortical (motor) potentials (Gemba *et al.*, 1979). At any rate, their results appear to indicate the presence of the superficial thalamocortical pathway to the primary somatosensory cortex which can elicit the surface negative-depth positive potential in the cortex of the monkey.

The main pathway for the generation of the positive potential in the frontal area contralateral to the stimulation seemingly passes directly from the thalamus to the frontal cortex, because a selective loss of the positive potential on the frontal area was observed in the cases with deep subcortical lesions, where the parietofrontal connection appeared to be intact (Cases 1, 2, 3). This view is consistent with the results obtained by animal experiments (Asanuma *et al.*, 1979, 1980).

The recent magnetoencephalographic study suggested that there appeared to be a tangential dipole in the central sulcus around 20 ms after stimulations of the median nerve (Wood *et al.*, 1985), but how much such a tangential dipole contributes to the SEPs is still unclear. Since magnetoencephalography is based on the recording of a tangentially oriented dipole (Hari *et al.*, 1984; Rose *et al.*, 1987), a radially oriented dipole as postulated in this study would not be clearly detectable in the magnetic recording.

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X-LINKED DOMINANT HEREDITARY MOTOR AND SENSORY NEUROPATHY

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SUMMARY

Modern techniques have defined the hereditary motor and sensory neuropathies (HMSN) as a genetically heterogeneous group of disorders. This includes a rare variant with X-linked dominant inheritance. We have traced this disorder through 6 generations of a large Canadian kindred; neurological and electrophysiological examinations were performed in 57 family members and nerve biopsies were studied in 2 affected males, early and late in the disease; 42/83 family members were affected. No male-to-male transmission was encountered in 19 sons of affected fathers, whereas all their daughters expressed the disease. Linkage was shown to the DNA loci DXYS1 $Z_{\max} = 2.87$ at $\theta_{\max} = 0.06$ and to PGK1 $Z_{\max} = 1.51$ at $\theta_{\max} = 0$ (Beckett *et al.*, 1986). The typical clinical features are onset in early childhood, pes cavus, atrophy and weakness of peroneal muscles and intrinsic hand muscles, and sensory abnormalities. Males were severely affected, whereas females had mild or subclinical disease. Electrophysiological observations indicated a substantial loss of distal motor and sensory nerve fibres. Evoked compound muscle action potentials in extensor digitorum brevis were absent or severely reduced in 42% of cases and the peroneal motor nerve conduction velocity was mildly reduced to a mean $36.5 \pm 7.4 \text{ m} \cdot \text{s}^{-1}$. Sural sensory nerve action potentials were absent or severely reduced in 75% of those affected. Nerve biopsies showed loss of myelinated and unmyelinated nerve fibres, regenerative sprouting and secondary demyelination. The findings indicate that this distinct variant of HMSN is the result of primary axonal degeneration.

INTRODUCTION

A familial disorder of peroneal atrophy, pes cavus and late claw hand formation was first described, independently, by Charcot and Marie (1886) and by Tooth (1886). It has since been recognized that this clinical phenotype represents a genetically heterogeneous group of disorders (*see* historical review by Harding and Thomas, 1980*b*). Current classifications into hereditary motor and sensory neuropathies (HMSN) types I and II are based on criteria originally defined by Dyck and Lambert (1968*a, b*), which were confirmed by Thomas and Calne (1974) and Buchthal and Behse (1977). Both types display autosomal dominant and less frequently, autosomal recessive inheritance (Harding and Thomas, 1980*a*). Additional genetic heterogeneity has been shown for HMSN type I, with respect to linkage to the Duffy blood group locus on chromosome 1 (Bird *et al.*, 1982; Guiloff *et al.*, 1982; Dyck *et al.*, 1983*a*) and to markers on chromosome 17 (Vance *et al.*, 1989). Gene expression is highly variable, as is often the case in autosomal dominant disorders, leading to a considerable variability of clinical severity in members of one family (Dyck *et al.*, 1983*b*). Males are often more severely affected than females (Harding and Thomas, 1980*b*) which is reflected in the preponderance of affected males in early reports based primarily on clinical observations (Herringham, 1889).

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The possibility of X-linked inheritance has been suggested in a few early reports (Allan, 1939; Erwin, 1944; Woratz, 1964). This conclusion was met with justified scepticism (Harding and Thomas, 1980a) since it was based primarily on clinical observations and lacked supporting laboratory evidence. Extended investigations of these families with modern DNA technology have now provided further evidence in support of an X-linked transmission (Gal *et al.*, 1985; Beckett *et al.*, 1986; Rozear *et al.*, 1987; Ionasescu *et al.*, 1988).

This report concerns a large Canadian kindred of 6 generations with a familial motor and sensory neuropathy, conforming to a pattern of X-linked dominant inheritance. Tight linkage was found to the DNA loci DXYS1 and PGK1, located on the proximal long arm of the X-chromosome (Beckett *et al.*, 1986). The phenotypic expression of this mutation resembles HMSN type I, yet electrophysiological and pathological findings are those of a primary axonal degeneration.

METHODS

Subjects

Sixty family members were examined personally in a full neurological examination and electrophysiological studies were performed in 57. Reliable medical records were available for 17 additional family members; 3 individuals, offspring of an unaffected female (II.5), were interviewed by telephone. Historical data on deceased individuals were verified by several living family members.

Electrophysiological studies

Motor conduction studies. Maximum motor nerve conduction velocity (MNCV) and distal motor latency (DML) in the peroneal nerve on recording from extensor digitorum brevis (EDB) were measured with stimulation at the popliteal fossa, fibular head and ankle. Anterolateral compartment motor fibres were also assessed by stimulating the common peroneal nerve at the popliteal fossa and fibular head and recording over the anterior tibial and peroneal muscles, respectively. The stimuli were adjusted to just supramaximal levels to ensure a maximum compound muscle action potential (CMAP). Recordings were made with surface electrodes.

Sensory conduction studies. Maximum sensory conduction velocity was measured in the superficial peroneal or sural nerves. Antidromic recordings were made with bipolar surface electrodes and the respective nerves were stimulated just supramaximally at two sites, 5 to 10 cm proximal to the recording electrode, and another 10 cm more proximally. Maximum sensory conduction velocity was measured between the two stimulus sites.

Other electrophysiological studies. In instances where the maximum EDB CMAP was 0.5 mV or less in peak-to-peak amplitude, a motor unit estimate was carried out (McComas *et al.*, 1971). Needle electromyography from EDB, tibialis anterior, extensor digitorum longus, peroneus longus, and gastrocnemius muscles was performed when the MNCV and/or CMAP were reduced.

Pathological assessment

Biopsy of the superficial and deep peroneal nerves at the ankle was performed in IV.1 and VI.3. The nerves were fixed in 2.5% buffered glutaraldehyde and processed according to standard techniques for light and electron microscopy and teased fibre preparations (Dyck *et al.*, 1984). Morphometric analysis was performed using a Zeiss Videoplan. Teased fibres were graded according to Dyck *et al.* (1984). The unmyelinated nerve fibre density and the frequency of regenerating fibre clusters were estimated from serial electron micrographs. A muscle biopsy was obtained from the tibialis anterior muscle. Frozen sections were stained with haematoxylin and eosin, Gomori trichrome, DPNH, ATPase and PAS.

Molecular genetic studies

Linkage analysis with 10 X-chromosome specific DNA probes was performed in 35 family members of generations III–V. Standard methods were used for DNA extraction, Southern blots and hybridization, and linkage analysis. Details have been published (Beckett *et al.*, 1986).

RESULTS

We have traced the disorder through 6 generations (fig. 1) and have personally studied 57 individuals clinically and electrophysiologically. Unavailable family members were interviewed by telephone and medical records were obtained for ascertainment of disease. Of the 83 family members for whom reliable data were obtained, 42 were affected. Of those personally examined 19/28 females and 13/32 males showed signs of disease. Affected females transmitted the disorder to approximately half of their offspring of either sex. Affected males, however, transmitted the disease to *all* of their 11 daughters, but to *none* of their 19 sons. (V.38, V.39 and VI.33–35 are 2–5 yrs old and although clinically normal and presumed unaffected, they are too young for a reliable ascertainment of disease status.) The lack of male-to-male transmission and the 1:1 ratio of affected versus unaffected family members, suggest an X-linked dominant mode of inheritance.

Linkage analysis

A systematic linkage analysis was performed in 35 members of generations III–V (indicated by arrow on the pedigree in fig. 1), with 10 X-chromosome specific DNA probes of known regional assignment. The results of this study have been published previously (Beckett *et al.*, 1986) and will only be summarized. Close linkage was observed with the DNA marker loci, DXYS1 and PGK1, by a maximum lod score of 2.87 and 1.51 respectively, at a maximum recombination fraction of 0.06 and 0, respectively. This suggested a localization of the mutation on the proximal long arm of the X-chromosome near Xq 13 (Page *et al.*, 1982; Hutz *et al.*, 1984; Drayna and White, 1985).

Clinical observations

A summary of the clinical findings of affected males and affected, probably heterozygous females is given in the Appendix. We have employed criteria for grading similar to those used by Rozear *et al.* (1987), to allow a comparison with their findings. Representative case reports for affected males are given for IV.1 and VI.3 from whom nerve biopsies had been obtained. Case reports for V.1 and V.4 are typical of the less severe expression of disease in heterozygous females.

IV.1 (fig. 2) was examined at age 61 yrs. The onset of symptoms dated back to early childhood when he noted awkwardness and difficulty in running. He always had high arched feet. In his teens, the muscles in his lower legs became thin and he frequently twisted his ankles. His penmanship was always poor and his fingers and hands were clumsy, particularly in cold weather. Over the years, his symptoms progressed quite insidiously and he developed pain and sensations of pins and needles in his feet and intermittently in his fingers. The hand muscles became progressively wasted, and his fingers clawed, so that he had very poor use of his hands and was now restricted to signing his name. A triple arthrodesis, performed in both feet at age 38, improved his walking. Yet in the last 10 yrs, walking had become more difficult and he has had to use two sticks. On examination there was marked wasting and weakness of the hand muscles, in particular the thenar muscles and of all muscles below the knee. There was pes cavus and varus deformity. Tendon reflexes were depressed in the arms and at the knees and ankle jerks were absent.

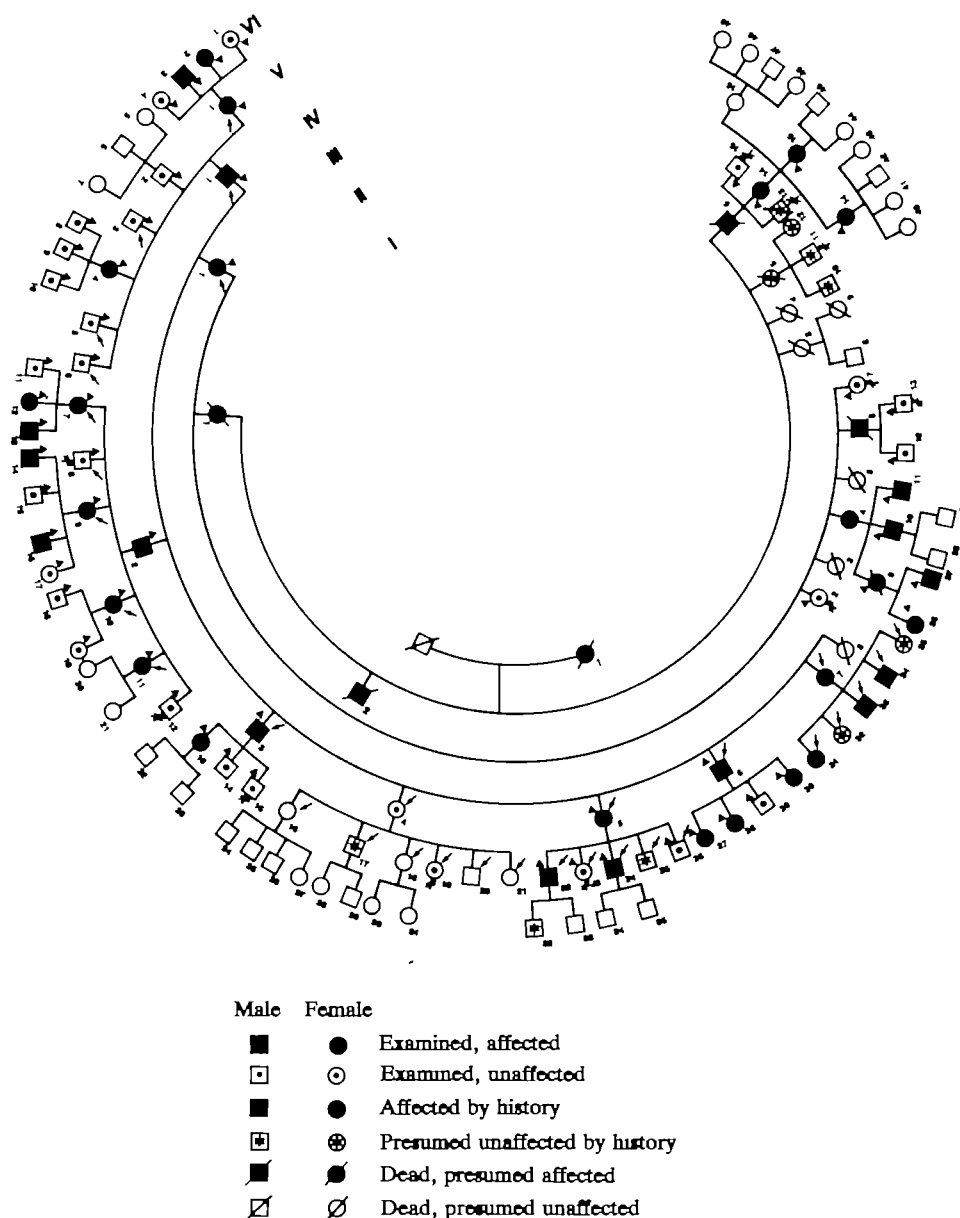


FIG. 1. Pedigree of the family showing X-linked dominant inheritance. Electrophysiological examinations were performed in individuals marked with a triangle. Family members taking part in the linkage analysis are marked with an arrow. Offspring of unequivocally normal family members are not illustrated (≠)

There was a graded loss of all sensory modalities to just above the wrist and to the knee. His gait was unsteady with bilateral foot drop.

VI.3 was examined at age 14 yrs. He had difficulty running even when in kindergarten, when his feet were already high arched. At age 8–10 his gait became increasingly awkward. He tripped easily and tended to walk on the lateral edge of the foot. He had difficulty using his hands in cold weather and needed help



FIG. 2. *Case IV.1*, aged 61 yrs. Illustration of the clinical phenotype. Note the advanced atrophy of distal leg muscles with pes cavus.

with shoelaces and buttons. On examination, there was mild wasting and weakness of the hand muscles, in particular the thenar muscles. His feet were high arched with marked hammer toe formation and extensive callosities on the lateral foot borders. Peroneal and anterior tibial muscles, and to a lesser extent the gastrocnemius muscles were wasted and he was unable to dorsiflex his ankle. His tendon reflexes were depressed and the ankle jerks were absent. All modalities of sensation were reduced to wrist and midcalf levels. Cutaneous nerves were not enlarged.

V.1, the 37-yr-old mother of *VI.3*, was clumsy when running as a child and was never able to ice skate. In her late teens her fingers felt awkward in cold weather and she had trouble doing up buttons. Her feet were always high arched but recently she developed increasing hammer toes and she had a tendency to sprain her ankles. Her feet became numb. The examination showed moderate wasting of the intrinsic hand muscles and the thenar eminences and moderate wasting and weakness of the peroneal muscles and small foot muscles with pes cavus and hammer toe formation. Ankle jerks were absent and sensation was reduced to the wrists and ankles. She walked with a mild steppage gait.

V.4 was examined at age 29 yrs. She had high arched feet since childhood, was unable to ice skate and had slight difficulty walking on uneven ground with a tendency to trip. The examination showed slight wasting and weakness of intrinsic hand muscles, highly arched feet and hammer toe formation, but only a little weakness in ankle dorsiflexion and eversion. Ankle jerks were absent and there was a mild impairment of sensation in her toes and soles. Her gait was normal.

The onset of clinical symptoms, therefore, dates back to early childhood. Males were much more severely affected than females, and all but 2 had symptoms in the first decade. A considerable gait disturbance was present in most males by the end of the second decade. Later in life, their gait was severely impaired and they required the aid of one or two sticks, but did not become wheelchair-bound. Only 4/23 affected females had moderate ankle weakness with a tendency to trip. As yet none has required orthopaedic

foot correction or aids. Most women had very mild symptoms, first noted towards the end of the second decade.

Symptoms and signs of hand muscle involvement, in particular of the thenar muscles, occurred early. They were noted by most males in the early teens and often progressed to severe weakness and claw hand deformity. Clumsiness and sensory symptoms were noted in hands and feet, most commonly in cold weather. All modalities of sensation were reduced.

Electrophysiological observations

Findings in affected family members

Peroneal motor nerve conduction. MNCV for fibres to EDB was moderately slowed as compared with that for unaffected family members and of healthy controls (fig. 3).

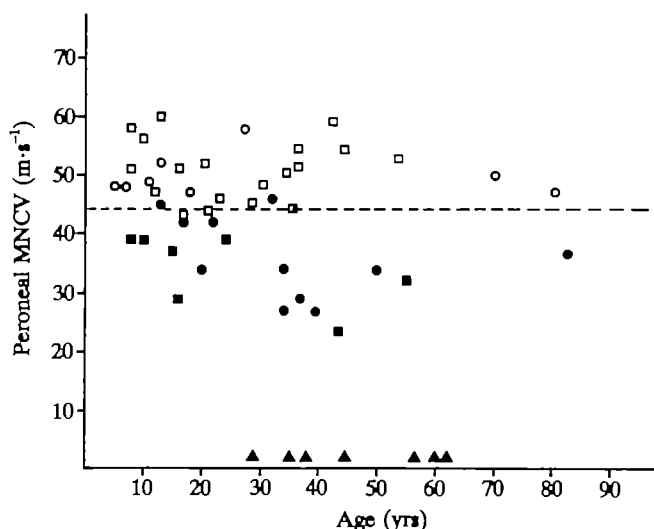


FIG. 3. Peroneal motor nerve conduction velocity (MNCV) for fibres to extensor digitorum brevis muscle of unaffected (open symbols) and affected (solid symbols) members from the kinship with X-linked dominant HMSN. No response was recorded in 2 females and 5 males (closed triangles). The interrupted line represents the lower limit of normal + 2 SD.

In 7 cases no EDB response was obtained. In 6 others, the CMAP for EDB was very small (≤ 0.5 mV) and the motor unit counts were severely reduced (4, 2, 2, 2, 1 and 1, respectively). Despite such severe losses of motor fibres, MNCV was normal (44 m.s^{-1}) in 1 case, with a single remaining motor unit. In the others, a mild reduction in MNCV (36 m.s^{-1}) was seen in 1 case, and modest reductions of MNCV ($20\text{--}29 \text{ m.s}^{-1}$) in 3 others. In the 15 cases, where the EDB CMAP fell within the normal range (≥ 2.0 mV), MNCV was normal ($\geq 40 \text{ m.s}^{-1}$) in 6 cases, was mildly reduced ($30\text{--}39 \text{ m.s}^{-1}$) in 8 cases and more severely reduced (27 m.s^{-1}) in only 1 case.

Motor conduction in the shorter fibres of the peroneal nerve to the anterolateral

compartment muscles was assessed in 19/31 cases. An evoked potential was recorded in 12/13 cases with either absent or severely reduced EDB responses. Potential sizes were greater than the lower limit for controls (≥ 4.0 mV) in 9 (75%), and the MNCV exceeded the lower limit of the control range (≥ 40 m·s⁻¹) in 5 (41.7%). The potential amplitude exceeded the lower control limit in 5 of the 6 remaining cases; the MNCV was normal in 3 cases, mildly reduced (30–39 m·s⁻¹) in 2 and moderately reduced (29 m·s⁻¹) in only 1 case.

Needle electromyography. Increased amplitude of single motor unit action potentials was detected by needle EMG in all cases where the maximum CMAP in EDB or the anterolateral lower leg muscles was reduced or where the MNCV was slowed.

Sensory conduction. Sensory nerve action potentials (SNAPs) were unobtainable in the superficial peroneal or sural nerves in 19/28 cases in whom sensory conduction was measured. Maximal sensory conduction velocity was below normal (< 30 m·s⁻¹) in 1 case and the SNAP was abnormally reduced (< 5 μ V) in one case. The findings were thus abnormal in 21/28 cases (75%).

Sensory fibres in the sural and superficial peroneal nerves are similar in length to peroneal motor fibres to EDB, and probably suffered an equivalent loss. For example, SNAPs were absent in 6/7 cases with an absent EDB response (sensory conduction was not checked in the seventh case). In cases with fewer than 5 motor units in EDB, the SNAPs were absent in 5 and at the lower limit of normal with respect to amplitude in the remaining case. In the 15 cases in which the EDB CMAP potentials fell within the normal range, SNAPs were normal in 8, reduced in 1 case and absent in 6 cases.

Findings in unaffected family members

Peroneal motor nerve conduction. The amplitude of the EDB CMAP was above the lower limit of the normal range (≥ 2 mV) in 19/19 males and 7/7 females, and EDB MNCV was above the lower limit of normal (> 40 m·s⁻¹) in all 26 unaffected members.

Sensory conduction. Sensory conduction velocity was normal in all 24 members. Sural or superficial peroneal SNAPs were normal (≥ 5 μ V) in 21/24; the amplitude was reduced in 2 elderly individuals, and no response was obtained in one 80-yr-old woman.

Summary

In 28/31 affected cases, electrophysiological studies were abnormal, based on reductions in peroneal MNCV for fibres to EDB and/or the anterolateral lower leg muscles, reductions in the amplitude of the CMAP for these muscles, or abnormal SNAP amplitude or conduction velocity. In 1 other case, the EDB motor unit number estimate was clearly reduced (12) and in yet another case, fibrillation was detected in the EDB. Overall, at least one parameter was abnormal in 30/31 affected cases (96.8%). The recordings were normal only in 1 affected male, studied when aged 3 yrs, who now has advanced clinical signs, but was not available for reexamination.

Modest reductions in MNCV were characteristic of this disorder and paralleled changes in the CMAP amplitude for EDB and the anterolateral muscles. Peroneal MNCV was above 30 m·s⁻¹ in 55% for motor fibres to EDB and in 90% of those to the anterolateral muscles. Potential amplitudes were better preserved in the latter.

Pathological observations

Transverse sections of the superficial and deep peroneal nerves from VI.3 (fig. 4A) and from IV.1 (fig. 4B) revealed a moderate to marked loss of myelinated nerve fibres, with abundant evidence of regenerative sprouting. Thinly myelinated regenerating fibres were typically clustered and surrounded by concentrically arranged Schwann cell processes (fig. 4C) (cluster density: VI.3 = 190/mm²; IV.1 = 1080/mm²). As a result there was a predominant loss of largely myelinated fibres and a shift of the fibre histogram to the smaller fibre range. This was also true for the unmyelinated fibres, which showed a progressive loss of larger unmyelinated axons with duration of the disease and an increase in smaller axons (fig. 5). Electron microscopy revealed Schwann cell plates which were indicative of chronic fibre loss. Analysis of randomly selected teased fibres (Table 1) showed evidence of demyelination/remyelination (categories C, D, F; Dyck *et al.*, 1971, 1984) clustered along myelinated nerve fibres; this was suggestive of secondary demyelination.

Biopsies of the tibialis anterior muscles showed large and small grouped muscle fibre atrophy of both type I and type II fibres, indicating chronic ongoing denervation.

DISCUSSION

Observations obtained from part of this large kindred resulted in one of the first reports suggesting the possibility of an X-linked dominant mutation on the basis of genetic evidence (Beckett *et al.*, 1986). We have extended the investigation to many more family members in order to define the clinical and neurophysiological characteristics, the pathological features, and the natural history of this variant of HMSN. The X-linked dominant mode of inheritance was confirmed in 6 generations.

Three very large pedigrees have now been reported in which this mode of inheritance was established by clinical examination and modern DNA technology (Allan, 1939; Woratz, 1964; Gal *et al.*, 1985; Beckett *et al.*, 1986; Rozear *et al.*, 1987). Linkage studies, using the same X-chromosome specific DNA marker DXYS1, identified a fourth family, yet the report gives little clinical detail (Ionasescu *et al.*, 1988). Conclusions on a kinship reported by Phillips *et al.* (1985) are tentative, since only few offspring of affected males had complete examinations, and linkage studies were not performed. The report by Fischbeck *et al.* (1986) documented 4 families with suggested X-linked inheritance. Family 2 is identical with that described by Rozear *et al.* (1987), yet differences in the pedigree and in the reported lod scores are noted. Families 3 and 4 are small and few clinical details are provided (Fryns and Van den Berghe, 1980). Most unusual is family 1 in this report which, according to a more detailed earlier description (Cowchock *et al.*, 1983), bears little resemblance to Charcot-Marie-Tooth disease. What is described is a more generalized neurodegenerative disorder with widespread motor and sensory deficits, deafness and mental retardation beginning in infancy. Although the pattern of linkage was seemingly similar to X-linked dominant HMSN, the two conditions are not likely to be genetically the same.

There is strong evidence for linkage of the X-linked dominant HMSN to the DNA markers DXYS1 and PGK1, which have both been mapped to the Xq13 region on the proximal long arm of the X-chromosome (Hutz *et al.*, 1984; Drayna and White, 1985). Combining the data of the reported 4 large families establishes cumulative lod scores

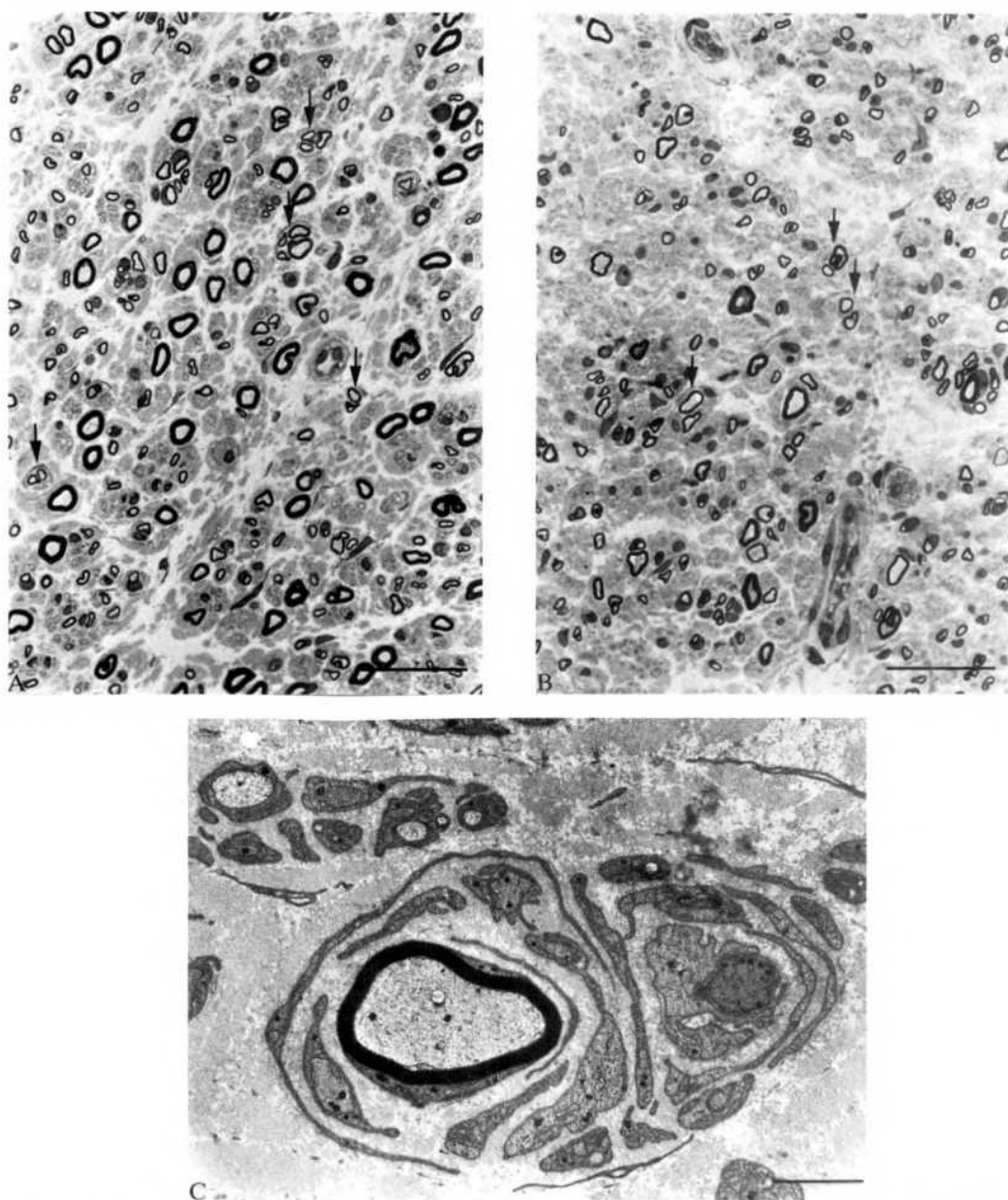


FIG. 4. Transverse sections of the superficial peroneal nerves. A, from Case VI.3 at age 16 yrs, and, B, Case IV.1 at age 61 yrs. Note the progressive loss of myelinated fibres with age and the numerous clusters of regenerated, thinly myelinated nerve fibres (arrows). Epon section, toluidine blue. Bar = 100 μ m. C, electron micrograph illustrating a regenerative cluster. The abutting Schwann cell processes resemble an onion bulb formation. Bar = 3 μ m.

for DXYS1 and PGK1 at $\hat{Z}$ max = 8.196 at $\hat{\Theta}$ max = 0.10 and $\hat{Z}$ max = 3.19 at $\hat{\Theta}$ max = 0.05, respectively, providing strong evidence for linkage.

The phenotypic expression of this mutation is consistent within the reported families

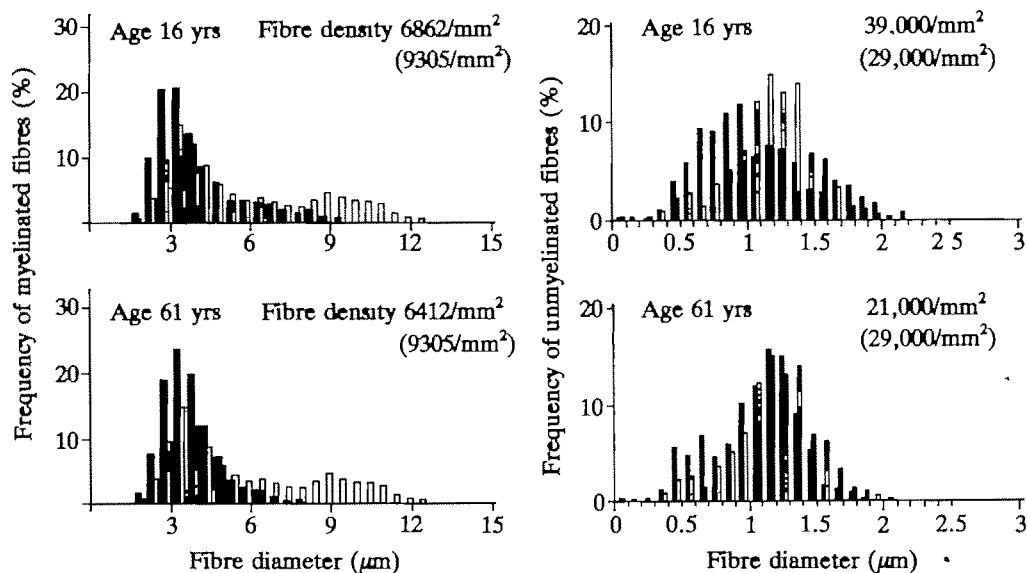


FIG. 5. Histograms of myelinated (*left*) and unmyelinated fibres (*right*) in the superficial peroneal nerve for Cases VI.3 (*upper*) and IV.1 (*lower*) showing a greater loss of large myelinated and unmyelinated axons in the latter. The increased number of smaller axons reflects abundant nerve fibre regeneration (open bars = control).

TABLE 1. TEASED FIBRE ANALYSIS (SUPERFICIAL PERONEAL NERVE)

Case	Grading*						n
	A + B	C	D	E	F	G	
VI.3	52	13	11	2	22	—	122
IV.1	78	3	9	1	9	—	140

* Percentage values; n = number of teased fibres. Categories A + B = normal; C, D, F = paranodal and segmental demyelination and remyelination; E = axonal degeneration (Dyck *et al.*, 1971, 1984).

and resembles that of the dominant form of HMSN type I. Males, with few exceptions, are much more severely affected and become symptomatic during the first decade. Affected females, for the most part, show only mild signs of disease. They date the onset of symptoms to the end of the second decade or later, as is illustrated in our review and elaborated in more detail by Woratz (1964). Atrophy of the small foot and peroneal muscles progresses insidiously and leads to pes cavovarus and hammer toe formation. This may result in a severe gait disturbance by the fifth and sixth decades. Atrophy of thenar muscles and intrinsic hand muscles is a constant and early feature resulting in decreased dexterity and crippling deformity of the hands in advanced disease. Sensory abnormalities are found consistently, even in mild cases, and are particularly noted in cold weather. Patients with very mild physical signs admitted to symptoms during exposure to cold. This accentuation of neuropathic symptoms in the cold was particularly

emphasized by Woratz (1964). His detailed clinical account of a large German family coincides with our observations and those of Allan (1939) and Rozear *et al.* (1987). Interestingly, Woratz observed severe neuropathic signs and foot deformities in 6/27 women examined late in life. This may relate to a difference in age at the time of examination and may also have been influenced by environmental factors, as was stated by the author.

Electrophysiological data and pathological observations have only been reported for the large family with German ancestry studied by Rozear *et al.* (1987). Their findings are in accord with our observations but we differ in the interpretation.

In affected males, Rozear *et al.* recorded no response with stimulation of peroneal motor fibres in all cases and with stimulation of median motor fibres in two-thirds of the cases studied. Conduction velocities, when recordable, were moderately reduced in median and ulnar motor fibres, but patients were said to have had a severe functional deficit with atrophy of thenar muscles and intrinsic hand muscles and presumably had considerable loss of motor fibres. No data were provided for distal latencies, CMAP amplitudes, and observations made by needle electromyography. Sensory conduction was not examined or was not reported.

The authors correlated the findings of reduced motor conduction velocity with the pathological changes in a sural nerve biopsy, which they interpreted as being 'characteristic' of a hypertrophic demyelinating neuropathy'. We disagree with this interpretation and conclusion and, in this report, provide detailed evidence which characterizes this disease as a primary axonal neuropathy.

Our electrophysiological observations clearly indicated a substantial loss of distal motor and sensory fibres. This was illustrated by the absence or severe reduction of the EDB CMAP amplitude in 13/31 (42%) affected individuals, and the very low EDB motor unit counts. Correspondingly, findings on needle electromyography suggested chronic ongoing partial denervation and reinnervation. The abnormalities in sensory fibres of similar length (sural and superficial peroneal nerve fibres) paralleled findings in EDB motor conduction. Sural SNAPs were absent or severely reduced in size in 21/28 (75%) affected individuals. These observations were supported by the findings in the nerve and muscle biopsies.

A modest slowing of conduction velocity, to the same degree as observed by Rozear *et al.*, was recorded primarily in distal motor fibres of the peroneal nerves. Recordings from more proximal motor fibres of the same nerve, namely those supplying the anterior and lateral compartment muscles, showed only mild slowing. Conduction slowing therefore reflected primarily motor fibre loss and possibly to some degree, secondary myelin changes. The modest reductions in motor conduction velocity could be explained by loss of the largest and fastest conducting nerve fibres on chance alone. Alternatively, axonal tapering and/or secondary demyelination, perhaps in combination with a loss of faster conducting fibres, could have contributed to the slowing of motor conduction. Examination of teased fibres revealed clustering of demyelination along the length of nerve fibres, implicating axonal influences and pathology (Dyck *et al.*, 1971, 1984).

The appearances in the nerve biopsies were very similar to those illustrated by Rozear *et al.* (1987). The findings indicated a considerable loss of large myelinated nerve fibres and ample nerve fibre regeneration. Clusters of thinly myelinated, regenerating nerve fibres were surrounded by concentric Schwann cell processes,

resembling onion bulb formations. In addition, examination of the biopsy by electron microscopy and morphometric measurements clearly demonstrated a loss of large myelinated and unmyelinated nerve fibres.

The electrophysiological and morphological findings thus support the concept that this hereditary neuropathy is the result of a primary axonal or neuronal degeneration. As such, the pathological and physiological abnormalities resemble those of the dominant form of HMSN type II. Yet the clinical features of this distinct variant of peroneal atrophy resemble those of the HMSN type I.

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APPENDIX CLINICAL FEATURES OF AFFECTED INDIVIDUALS WITH X-LINKED HMSN

Case	Age at onset* (yrs)	Age at exam or death	Motor UEs	Motor LEs	Pes carpus	Sensory loss	DTR UEs	DTR Knees	DTR Ankles	Gait disturbance	Overall involvement
Affected males											
IV.1	8	61	2	1	+	4+	1+	1+	0	3+	3+
IV.2	8	60	2	0	+	4+	0	1+	0	3+	3+
IV.3	50	55	4	4	+	0	2+	1+	0	2+	2+
IV.6	10	44	2	0	+	4+	1+	1+	0	3+	3+
IV.10	10	44	2	2	+	4+	1+	0	0	2+	2+
IV.11	8	43	2	1	+	4+	0	0	0	2+	2+
V.22	Teens	35	4	4	+	0	NA	NA	0	1+	1+
V.24	Teens	21	5	4	+	0	2+	1+	0	1+	1+
V.33	12	21	3	2	+	NA	NA	NA	0	3+	2+
V.34	12	20	4	3	+	NA	0	1+	0	2+	2+
V.37	11	12	4	3	+	1+	1+	1+	0	1+	1+
VI.3	10	13	4	3	+	1+	2+	2+	0	3+	2+
VI.14	10	14	5	4	+	0	1+	1+	0	1+	1+
VI.16		6	5	4	0	0	1+	0	0	0	1+
Affected males by HX											
II.2	Childhood	NA	1	0	+	NA	NA	NA	NA	4+	4+
II.6	Childhood	73	2	0	+	NA	NA	NA	NA	4+	3+
III.6	Childhood	53	2	0	+	NA	NA	NA	NA	4+	4+
Heterozygous females											
III.1		82	3	3	+	4+	1+	0	0	Wheelchair (amputation)	2+
III.14		NA	3	3	+	2+	1+	1+	0	1+	2+
IV.5		47	5	4	+	0	2+	2+	1+	0	1+
IV.9		31	4	3	+	3+	1+	1+	0	1+	Dead
IV.14		37	5	5	0	1+	2+	2+	1+	0	1+
IV.15	Teens	35	5	4	+	3+	1+	1+	0	1+	1+
V.1	10	35	4	3	+	2+	2+	2+	0	2+	2+
V.4	10	29	4	4	+	1+	2+	2+	0	1+	1+
V.7	10	37	4	4	+	2+	1+	1+	0	1+	1+
V.9		29	5	4	+	0	2+	2+	1+	0	1+
V.10		27	4	4	+	1+	2+	2+	1+	0	1+
V.11		25	5	4	+	1+	2+	2+	0	1+	1+
V.27		20	4	3	+	2+	2+	1+	0	1+	1+

Case	Age at onset* (yrs)	Age at exam or death	Motor UEs	Motor LEs	Pos carus	Sensory loss	DTR UEs	DTR Knees	DTR Ankles	Gait disturbance	Overall involvement
V.28		18	4	4	+	1+	NA	NA	0	1+	1+
V.30		8	5	5	+	0	2+	2+	2+	0	1+
V.31		24	5	4	+	NA	NA	NA	NA	1+	1+
V.36		20	5	4	+	1+	0	0	0	0	1+
VI.2		16	5	5	0	1+	1+	2+	0	0	1+
VI.12		12	5	4	+	1+	1+	1+	1±	0	1+
Affected females by HX											
I.1		97	5	5	+	NA	NA	NA	NA	0	1+
II.1		69	3	4	+	NA	NA	NA	NA	1+	1+
III.4		76	5	4	+	NA	NA	NA	NA	1+	1+
IV.7		43	4	4	+	NA	NA	NA	NA	1+	1+
V.13	Teen	33	4	4	+	NA	NA	NA	NA	1+	1+

* No age entered when patient asymptomatic. Patient designation refers to fig. 1. UE = upper extremity, LE = lower extremity; DTR = deep tendon reflexes; NA = not available.

Degree of involvement

0 = none; 1+ = mild changes on exam only, no significant functional impairment, 2+ = obvious changes on exam, mild functional impairment—capable of gainful employment, 3+ = obvious changes on exam, moderate functional impairment, disabled for work. Capable of self-care or activities of daily living. 4+ = severe changes on exam, severe functional impairment, requires help with or incapable of self-care.

Weakness

Power rated as per the BMRC scale, ranging from 5/5 to 0/5. 5 = normal, 4 = power 4/5, no or mild atrophy; 3 = power 3/5, readily noticeable atrophy; 2 = power 2/5, marked atrophy; 1 = power 1/5, severe atrophy, little muscle tissue present, 0 = power 0/5, severe atrophy, no muscle tissue identifiable.

Sensory loss

0 = none, 1+ = no symptoms, mild changes on exam, usually loss of vibratory sense in the toes; 2+ = mild symptoms, more severe changes on exam, usually loss of all modalities distal to the ankles; 3+ = readily volunteered sensory complaints by history, severe loss of all modalities, usually below the knees, 4+ = severe symptoms, with complete or nearly complete loss of all modalities below the knees and severe involvement of the hands.

SELECTIVE SPATIAL ATTENTION IN PATIENTS WITH VISUAL EXTINCTION

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SUMMARY

The present study was designed to verify the attentional performance of patients with parietal lesions in the experimental condition in which they had to pay attention to 3 spatial positions located on the left, on the right and directly above the fixation stimulus (Experiment 1) and to only 1 of the 3 spatial positions at a time (Experiment 2). Twelve patients (6 subjects with right parietal lesions and 6 subjects without neurological deficits) participated in the experiment. The results of Experiment 1 showed that in patients with right parietal lesions the speed and accuracy of response to horizontally aligned stimuli increased gradually from right to left, whereas the control group showed only the effect due to the different retinal eccentricities of the 3 stimuli, that is, responses to central stimuli were faster and more accurate than responses to left and right stimuli. The results of Experiment 2 showed that both the neurological and control groups were faster to respond to central than to left and right stimuli, and that the neurological group was faster to respond to right than left stimuli, whereas no difference in RTs between two visual fields was obtained in the control group. Furthermore, when the patients had to respond to 3 spatial locations aligned horizontally (Experiment 1), the speed and accuracy of response to the right stimulus were the same as when they had to focus attention on it (Experiment 2). These results showed that the focus of attention in patients with visual extinction is on the rightmost stimulus and that the increased attention to the right is accompanied by a decreased attention to the left.

INTRODUCTION

Patients with posterior parietal injury may fail to report stimuli appearing in the visual field contralateral to the lesion when both visual fields are stimulated simultaneously (*see* De Renzi, 1982, for a review). This deficit is called visual extinction. If a single stimulus is presented to the left or right visual field (LVF or RVF), the same patients have no difficulty reporting its occurrence. The speed of response to stimuli presented to the hemifield contralateral to the lesion is, however, largely slower to that of response to stimuli presented to the ipsilateral hemifield (Posner *et al.*, 1984, 1987; Làdavas, 1987; Làdavas, *et al.*, 1989). An explanation given for visual extinction is that it is an attentional deficit which specifically involves the orienting component of attention. Posner *et al.* (1984), Baynes *et al.* (1986) and Morrow and Ratcliff (1987) have shown that if the patients are instructed to attend selectively to the impaired hemifield, the difference in speed of response between the two visual fields becomes very small.

More recently, Làdavas (1987) has shown that in patients with right parietal lesions the reduced ability to shift attention from one location in space to another is not strictly tied to retinotopic coordinates. By measuring reaction time (RT) to a light stimulus presented in one of two horizontally aligned positions within each visual field, it was

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shown that the responses to stimuli presented to the LVF were slower than responses to stimuli presented to the RVF. Further, the stimulus which occupied a relative left position yielded longer RTs than the stimulus which occupied a relative right position, independent of which visual field was stimulated. Similar results were obtained by Posner *et al.* (1987) using a 'cuing' paradigm.

Two different hypotheses can be formulated to explain these results. Both share the above mentioned hypothesis that in patients with right parietal lesions orienting attention towards the left is impaired and therefore all responses which require a left shifting of attention are delayed or omitted. The two hypotheses, however, make different assumptions as to where the focus of attention is allocated before there is a need for the subjects to shift their attention towards the stimuli which require a manual response. In fact, a stimulus must enter the focus of attention and become conscious before an arbitrary response, that is one not automatically triggered by the stimulus, can be emitted (Posner, 1980, 1982).

The first hypothesis assumes that in patients with parietal lesions the focus of attention is consistently caught by the stimulus position ipsilateral to the lesion. The displacement of the focus of attention to the most ipsilesional stimulus position creates a general facilitation of all responses potentially triggered from this location and a disadvantage or even exclusion of reactions to other stimulus locations. The second hypothesis assumes that when the patients have to respond to horizontally aligned visual stimuli they behave like normal subjects, i.e., they centre the focus of attention on a point halfway between the extreme spatial positions (Nicoletti and Umiltá, 1989). A stimulus appearing to the right of this attentional focus would call for a rightward shift of attention, and a stimulus appearing to the left of this attentional focus would call for a leftward shift of attention. Since in these patients leftward shifts of attention are impaired while rightward shifts are not, responses to left stimuli are delayed or even omitted, whereas responses to right stimuli are normal.

These two hypotheses were tested in Experiment 1 by studying visuomotor RT of patients with a right parietal lesion to three stimuli horizontally aligned above the fixation mark. The stimuli were located one on the left, one on the right, and a third directly above the fixation mark. If the focus of attention is caught by the stimulus ipsilateral to the lesion, a facilitation of processing at the rightmost location and a cost for the responses to the other two spatial positions would be expected. Conversely, if the focus of attention is on a point halfway between the two positions, an advantage for the middle position over the other two locations would be expected because of its proximity to the focus itself. Moreover, due to the reduced ability of these patients to shift attention towards the left, responses to left stimuli should be slower than responses to right stimuli. Furthermore, if patients with right parietal lesions allocate the focus of attention to the rightmost stimuli when 3 spatial locations are horizontally aligned (Experiment 1), then the speed and accuracy of response to the right stimulus under this condition should be the same as when the patients have to focus attention only on the right stimulus position. Therefore, Experiment 2 was intended to study visuomotor RT to stimuli appearing in only 1 of the 3 spatial locations. The 3 stimulus locations were the same as in Experiment 1, but this time in each experimental condition the trials were blocked in such a way that the stimulus could appear only to the left, to the right, and directly above the fixation mark.

EXPERIMENT 1

Two groups, each of 6 subjects, selected from the inpatient population of the Burke Rehabilitation Center (see Table 1) were tested. The neurological group was composed of patients with a unilateral lesion of the right parietal lobe confirmed by CT. They extinguished to double simultaneous visual stimulation (see below), and none displayed evidence of neglect, visual impairment, and receptive or expressive language disturbance. The presence/absence of neglect was tested in a task requiring the crossing out of 40 lines dispersed apparently randomly over a page (Albert, 1973) and in a wide range of other tests, including drawing a tree, a house and a clock face from memory and copying. The patients were asked also to read sentences of different length. A patient was designated as having neglect if he or she demonstrated contralateral neglect on at least one of the above mentioned tests. The visual field was tested by campimetry and visual acuity evaluation and this selection defined a group of patients without visual field deficits. All the neurological subjects were right-handed, had a hemiplegia or a severe hemiparesis contralateral to the lesion and did not display psychiatric symptoms. The control subjects were inpatients of the Burke Rehabilitation Hospital without neurological or psychological disorders.

TABLE 1. SUMMARY OF CLINICAL DATA FOR PATIENTS WITH PARIETAL LESIONS AND CONTROL GROUP

<i>Case</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>Hand</i>	<i>Onset of illness</i>	<i>CT scan</i>
RP1	67	F	R	3 yrs	R parietal infarct
RP2	41	M	R	10 mth	R frontoparietal infarct
RP3	72	M	R	11 mth	R parietal infarct
RP4	78	M	R	8 mth	R internal capsule
RP5	64	M	R	2 yrs	R frontoparietal infarct
RP6	70	F	R	7 mth	R parietal infarct
C1	72	M	R		
C2	67	M	R		
C3	75	F	R		
C4	68	F	R		
C5	67	M	R		
C6	46	M	R		

Extinction test

Before the experiment, the presence of visual extinction was assessed in each subject. The computer-controlled visual display used for this purpose consisted of four 2.5 deg/side squares forming the corners of an imaginary 12.5 deg/side square around a central fixation point. A trial began with a continuously displayed central fixation stimulus followed by the presentation of 1 or 3 possible stimulus conditions; either 2 'X's were briefly displayed centred in 2 of the squares, or 1 'X' was displayed, or no 'X's were displayed. Each 'X' subtended 0.6×1.2 deg of visual angle and was displayed for 75 ms. The subject was required to point with the index finger of the right hand to the square where an 'X' had been displayed.

The extinction test consisted of 96 trials: 24 trials in which a single stimulus was presented 6 times in each of the 4 squares; 48 trials in which 2 stimuli were presented simultaneously, equally distributed across each of the 6 possible between and within-field combinations; and 24 trials in which no stimulus appeared (catch trials). Fifteen patients with parietal lesions performed this test: 6 consistently omitted stimuli on the left side (more than 20% of the stimuli), 5 omitted left-side stimuli only rarely (less than 5% of the stimuli) and 4 performed the task without omissions. Only patients who omitted more than 20% of the stimuli on the left side on between-field double presentations participated in the study. They omitted less than 5% of the stimuli on the side contralateral to the lesion on a single stimulus presentation, and consistently

detected single stimuli or between-field stimuli in the right visual field. The control subjects performed this test without omissions.

Apparatus

Stimuli were generated by an Apple II microprocessor and displayed on a 15 inch videomonitor. For experimental trials, a one-button response box was affixed to a table under the subject's right hand and connected to the computer. Subjects pressed the button with the index finger of their right hand. The computer recorded responses and latencies, and stored these data on magnetic disc for subsequent analysis. All displays were viewed from a distance of 40 cm under normal illumination.

Procedure

A central fixation stimulus and three 2.5 deg/side squares horizontally aligned above the fixation stimulus were continuously displayed throughout the experimental session. The squares were located on the left, on the right and directly above the fixation stimulus. The horizontal distance between the centres of the squares was always 6 cm. The distance between the centres of left and right squares and the fixation stimulus was 8.5 cm and subtended about 6° of visual angle. The distance between the centre of the central square and the fixation stimulus was 6 cm and subtended about 4° of visual angle.

Each trial began with the instruction to look at the fixation stimulus. Eye movements were monitored by the experimenter who sat in front of the patients in an advantageous position for the detection of eye movements. The patient was aware that the experimenter was monitoring eye movements and he/she was instructed to look at the fixation stimulus whenever an eye shift occurred. When accurate fixation was established, the experimenter initiated the trial from the Apple keyboard, a 100–700 ms variable delay elapsed, and a target appeared centred in one of the squares for 100 ms. Trials in which eye movements occurred were omitted from the analysis but not replaced. The subject was instructed to push the response button when the 'X' appeared in one of the 3 squares. Reaction times (RTs) were measured from the onset of the stimulus to the appropriate key press.

The responsiveness to stimuli in the 3 spatial positions was tested in 3 experimental sessions, which were carried out on 3 different days. Each experimental session consisted of 30 practice trials and 90 experimental trials. Trials were arranged in a quasi-random sequence: the probability of occurrence of a stimulus in each of the 3 positions was equal but no more than 3 consecutive stimuli could occur in the same spatial position. The subjects were not aware of the run length restriction.

Results

Only RTs between 100 and 2000 ms were included in the analysis. Also omitted from the analysis were trials in which RT fell within this range, but the subject responded incorrectly or an eye movement occurred. 'Incorrect' responses were those in which a response occurred, but RT exceeded 2000 ms, and those in which the subject failed to respond or anticipated the target. Average RTs of both right-damaged and control group for the 3 spatial positions appear in Table 2.

The mean RTs for each subject and for each condition were submitted to an analysis of variance with repeated measures using Stimulus Position (left, central, right) as a within-subjects factor and Group (patients with visual extinction and control group) as a between-subjects factor. The analysis revealed a significant main effect of Group [$F(1,10) = 36.65$, $P < 0.001$] with patients responding more slowly than control subjects (662 ms vs 327 ms, respectively). Also the interaction was significant [$F(2,20) = 12.87$, $P < 0.001$]. In patients with right parietal injury, RT to right stimulus (597 ms) was faster than RTs to the central stimulus (638 ms) [$t(5) = 3.20$, $P < 0.05$] and to the left stimulus (752 ms) [$t(5) = 4.28$, $P < 0.01$]; and RT to the central stimulus (638 ms) was faster than RT to the left stimulus (752 ms) [$t(5) = 3.02$, $P < 0.05$]. All subjects showed this pattern of results. Conversely, in the control group RT to the central stimulus (307 ms) was faster than RT to both the left (333 ms) [$t(5) = 4.91$, $P < 0.02$] and

TABLE 2 RESULTS FOR PATIENTS WITH EXTINCTION (RIGHT PARIETAL GROUP) AND CONTROLS IN EXPERIMENT 1*

	<i>Left stimulus</i>	<i>Central stimulus</i>	<i>Right stimulus</i>
Right parietal group	752 (74%) ±268, 445/1000	638 (91%) ±217; 342/750	597 (98%) ±211, 312/749
Control group	333 (94%) ±60; 263/392	307 (95%) ±47, 251/355	331 (98%) ±63; 278/365

* Reaction time (RT), percentage of correct responses, SD and ranges for each RT mean as function of stimulus position (left, central, right).

the right stimulus (331 ms) [$t(5) = 5.62$, $P < 0.01$], and there was no difference between RTs to the left and the right stimuli.

A similar analysis of variance was carried out on the arc-sine transformations of percentage of correct responses. 'Incorrect' responses were those in which a response occurred but RT exceeded 2000 ms, and those in which the subject failed to respond or anticipated the stimulus. The last two types of errors were very rare and accounted for less than 2% of the trials (*see* Table 2).

Analysis of the percentage of correct responses again yielded a significant effect of the interaction between Stimulus Position and Group [$F(2,20) = 5.12$, $P < 0.025$]. In patients' responses to the left stimulus (74%) were less accurate than responses to the right stimulus (98%) [$t(5) = 5.84$, $P < 0.01$] and to the central stimulus (91%) [$t(5) = 3.0$, $P < 0.05$]. Conversely, in the control group there was no significant difference between responses to left (94%), central (95%) and right stimuli (98%).

Discussion

The present experiment showed that, in patients with right parietal lesions, the speed and accuracy of response to horizontally aligned stimuli increased from right to left. Patients were faster and more accurate in responding to a right stimulus than to a central stimulus or left stimulus. Furthermore, RTs to a central stimulus were faster than to a left stimulus and longer than RT to a right stimulus. The neurological group therefore showed a facilitation of all responses triggered by the most ipsilateral stimulus and a disadvantage or exclusion of reactions to stimuli located to the left of this location. It is interesting to note that in these patients the attentional bias in favour of the right relative position produced attentional benefits which were strong enough to overcome any retinal effects. Conversely, the control group was faster and more accurate in responding to the central stimulus than to both left and right stimuli, with no difference between RTs to left and right stimuli. In other words, the control group showed only the effect due to the different retinal eccentricities of the 3 stimuli.

The results suggest that in patients with right parietal injury the focus of attention was not centred on a midpoint of stimulus array, but was allocated to the rightmost position such that shifting attention to the other locations delayed the responses.

In order to verify whether the attentional deficit also extends to focused attention, another experiment was run which specifically tested focused spatial attention. Experiment 2 was intended to study visuomotor RT to stimuli appearing in only 1 of 3 spatial locations in a block of trials. The 3 stimulus locations were the same as in Experiment 1, but

this time in each experimental condition the trials were blocked in such a way that the stimulus could appear only to the left, to the right, and directly above the fixation mark. Because in this experiment the task requires attention to be focused in only one spatial position at any time, and therefore no displacement of attention is required, only the eccentricity effect is expected, i.e., responses to a central stimulus being faster than responses to left and right stimuli. Furthermore, if patients with right parietal lesions allocate attention to the rightmost stimuli when 3 spatial locations are horizontally aligned (Experiment 1), then the speed and accuracy of response to the right stimulus in Experiment 1 should be the same as when the patients have to focus attention only on the right stimulus (Experiment 2).

EXPERIMENT 2

Subjects

The same 12 patients that participated in Experiment 1 served in this experiment.

Conditions and procedure

The apparatus and the procedure were the same as in Experiment 1, except that only 1 square was displayed at a time in each of the 3 conditions. The square was located on the left (Condition 1), on the right (Condition 3), and directly above the fixation stimulus (Condition 2). The responsiveness to each of the 3 locations was tested in 6 experimental sessions, which were carried out on 2 different days. Each experimental session consisted of 20 practice trials and 50 experimental trials.

Results

Mean RT was computed across sessions for each subject for each of the 3 experimental conditions. The general pattern of results showed a systematic difference between the results of the 3 different conditions in either group (*see* Table 3). An analysis of variance with Stimulus Position (left, central, and right) as within factor and Group (patients with visual extinction and normal subjects) as between factor was carried out. The analysis showed a significant effect of the Group factor [$F(1,10) = 11.19, P < 0.01$], with the control group being faster (300 ms) than patients with parietal injury (603 ms) and of Stimulus Position factor [$F(2,10) = 33.59, P < 0.001$] with RTs to the central stimulus (426 ms) being faster than RTs to the left (479 ms) [$t(11) = 4.79, P < 0.001$] or to the right stimulus (451 ms) [$t(11) = 4.77, P < 0.001$]. There was also a significant interaction [$F(2,20) = 10.18, P < 0.001$].

A paired *t* test showed that in patients with parietal lesions RTs to central stimuli (566 ms) were faster than RTs to left stimuli (647 ms) [$t(5) = 3.02, P < 0.05$] and to right stimuli (598 ms) [$t(5) = 3.44, P < 0.02$], and RTs to right stimuli were faster than RTs to left stimuli [$t(5) = 3.74, P < 0.02$]. The control group showed only an advantage of RTs to the central stimulus (286 ms) over those to the left (311 ms) [$t(5) = 4.04, P < 0.01$] or right stimulus (304 ms) [$t(5) = 4.72, P < 0.01$].

The difference between RTs to left and right stimuli was not significant; *t* tests showed that the difference between RTs to the central and left stimuli was greater in neurological than in control group (83 ms vs 26 ms) [$t(10) = 3.89, P < 0.01$], whereas the two groups did not differ for RTs to the central and right stimulus (32 ms vs 21 ms). Also

TABLE 3 RESULTS FOR PATIENTS WITH EXTINCTION (RIGHT PARIETAL GROUP) AND CONTROLS IN EXPERIMENT 2*

	<i>Left stimulus</i>	<i>Central stimulus</i>	<i>Right stimulus</i>
Right parietal group	647 (75%) ± 261; 340/763	566 (98%) ± 228; 314/662	598 (85%) ± 229; 323/715
Control group	311 (97%) ± 40; 262/371	286 (95%) ± 46; 258/348	304 (96%) ± 43; 263/361

* Reaction time, percentage of correct responses, SD and ranges for each RT mean as a function of stimulus position (left, central, right).

the difference between RTs to the left and right stimuli was greater in the neurological than in the control group (113 ms vs 7 ms).

A similar analysis of variance was carried out on the arc-sine transformations of percentage of correct responses. The analysis revealed a significant effect of the Group factor [$F(1,10) = 9.14, P < 0.025$] with the control group (96%) being more accurate than the neurological group (83%). The interaction was also significant [$F(2,20) = 10.68, P < 0.001$]. Patients with parietal damage were more accurate in responding to central than to left [$t(5) = 5.18, P < 0.01$] or right stimuli [$t(5) = 5.60, P < 0.01$], and to right than to left stimuli [$t(5) = 5.65, P < 0.01$]. Conversely, the response accuracy to the 3 stimuli did not differ significantly in the control group (see Table 3).

The results of Experiment 2 showed that both groups were faster and more accurate in responding to the central stimulus than to either the left or right stimuli and that the experimental group responded faster and more accurately to RVF stimuli than to LVF stimuli. In contrast, no difference between the two visual fields was obtained in the control group. The difference between RTs to the central and left stimulus was greater in the neurological than in the control group, whereas the two groups did not differ on the difference between RTs to central and right stimuli.

In order to verify a different left-right imbalance of attention in the two experiments, the results obtained in Experiment 1 were compared with the results obtained in Experiment 2. A two-way analysis of variance on the results for the neurological group, using Experiment (Experiments 1 and 2) and Stimulus Position (left, central and right stimulus) as main within factors, showed a significant effect of Experiment [$F(1,5) = 53.11, P < 0.001$], with Experiment 1 yielding slower RTs than Experiment 2 (662 ms vs 603 ms, respectively). Also the main effect Stimulus Position was significant [$F(2,10) = 30.07, P < 0.001$] due to the difference between RTs to LVF (699 ms) and RVF stimuli (598 ms) [$t(11) = 4.20, P < 0.01$] and to the difference between RTs to the LVF (699 ms) and central stimulus (602 ms) [$t(11) = 4.95, P < 0.001$]. No difference between RTs to central and RVF stimuli was obtained.

The interaction was also significant [$F(2,10) = 4.37, P < 0.05$] because responses in Experiment 2 were faster than in Experiment 1 both for LVF (647 ms vs 752 ms) [$t(5) = 2.91, P < 0.05$] and central stimuli (566 ms vs 638 ms) [$t(5) = 5.70, P < 0.01$]. Conversely, RTs to RVF stimuli in Experiments 1 and 2 were virtually the same (597 ms vs 598 ms).

The same analysis of variance carried out on the arc-sine transformation of percentage of correct responses revealed a significant effect of Experiment [$F(1,5) = 34.28,$

$P < 0.005$], with Experiment 2 yielding more correct responses than Experiment 1 (92% vs 83%). Also the main effect Stimulus Position was significant [$F(2,10) = 31.78$, $P < 0.001$] and it was due to the fact that patients were more accurate to respond to central than to left stimuli (90% vs 74%) [$t(11) = 4.11$, $P < 0.01$], and to right than to left stimuli (72% vs 74%) [$t(11) = 5.84$, $P < 0.001$].

The same analysis of variance carried out on the results of control group, revealed a significant effect of both Experiment [$F(1,5) = 10.25$, $P < 0.025$], with Experiment 1 (323 ms) yielding slower RTs than Experiment 2 (300 ms), and Stimulus Position [$F(2,10) = 16.30$, $P < 0.001$], with RTs to central stimulus (297 ms) being faster than both RTs to LVF (322 ms) [$t(11) = 6.57$, $P < 0.001$] and RVF stimuli (317 ms) [$t(11) = 6.86$, $P < 0.001$]. No difference between RTs to LVF and RVF stimuli was obtained. The interaction between Experiment and Stimulus Position was not significant.

A similar analysis of variance performed on sine-arc transformation of correct responses did not reveal a significant effect or a significant interaction.

Discussion

The results of Experiment 2 showed that when RTs in all spatial positions were collapsed, patients with right parietal lesion were slower than the control group. This deficit, which has been already described in the literature (Posner *et al.*, 1987) can be interpreted as a difficulty of these patients to maintain a high level of alertness. However, Lådavas *et al.* (1989) have recently pointed out that the difficulty in maintaining a high level of alertness is not a specific deficit of patients with right parietal lesions because patients with right temporal lesions also showed an overall increase of RT compared with patients with left temporal lesions. The overall increase in RT found in the present study is therefore best attributed to a disruption of arousal mechanisms localized to the right hemisphere (Tucker and Williamson, 1984) rather than to the right parietal lobe itself.

Experiment 2 was mainly intended to verify the attentional performance of patients with extinction in the experimental condition in which their attentional resources were highly allocated on one spatial position. The results showed an eccentricity effect both in experimental and control groups, i.e., RTs were faster to central stimuli than to the LVF and RVF stimuli. Moreover, patients with visual extinction were slower to respond to LVF than to RVF stimuli, whereas no difference in RTs between the two visual fields was obtained in the neurologically intact subjects. The results also showed that the difference between RTs to the central and left stimuli was greater in the neurological than in the control group, whereas the two groups did not differ for the difference between RTs to central and right stimuli.

Patients with parietal lesions therefore performed as the control group in allocating attention on the right, whereas they were worse in allocating attention on the left. Morrow and Ratcliff (1987), using the cueing paradigm, obtained a similar left side deficit. They found that in patients with right parietal lesions responses to valid contralateral targets (cue and target on the neglected side) were slower than those to invalid ipsilateral targets (cue on the neglected side, target on the nonneglected side) or to valid ipsilateral targets (cue and target on the intact side). Three interpretations are available for the reduced responsivity found in the present study for stimuli presented to the contralesional

hemifield. The first one implies that, although the task required attention to be focused on the left spatial position, the attentional resources of these patients were allocated on the fixation point. Due to the relative right position of the fixation point, all responses to LVF stimuli required a left shifting of attention which causes a delay or an omission of response. This interpretation makes the strong assumption that these patients are forced by the lesion to attend to a right position although they are aware that the targets can never appear at that position. This interpretation becomes more plausible when we consider that patients were requested to look at the fixation point for the duration of the experiment and that overt and covert attention are usually closely linked. Alternatively, the increase in RT and errors found in the present study for LVF stimuli can be explained with a deficit shown by patients with a right hemisphere lesion in maintaining a high level of alertness. It is possible that this difficulty becomes particularly evident for stimuli presented in the visual field directly connected with it. Finally, the reduced responsivity to LVF stimuli may be due to subtle sensory loss, even though the patients reported here did not have visual field deficits, as shown by campimetry and visual acuity evaluation. The present experiment cannot distinguish between the three hypotheses and further investigations are required in order to clarify the nature of the LVF deficit.

When the results obtained in each spatial condition in Experiments 1 and 2 were compared, it was observed that responses in Experiment 2 were faster and more accurate than responses in Experiment 1. This is because RT for the detection of unstructured targets in different extrafoveal locations is shorter at expected positions (Experiment 2) compared with a condition in which target expectancy is the same for all possible positions (Experiment 1) (Posner *et al.*, 1978, 1980). Moreover, due to the experimental design of the present study, Experiment 1 was run before Experiment 2 and therefore the effect also can be explained by a practice effect. A most interesting result, however, is that the efficiency of responses to a right stimulus in the two experiments is the same, despite the fact that responses were faster and more accurate in Experiment 2 than in Experiment 1. These results suggest that patients with right parietal lobe lesions allocate the attentional resources to the rightmost position any time the visual stimuli are displayed along the horizontal dimension. This attentional bias for the rightmost stimuli can also account for the different responses to central stimuli in Experiments 1 and 2: when the central stimulus was located to the left of the right stimulus (Experiment 1) RTs to central stimuli were longer than RTs to right stimuli and shorter than RTs to left stimuli. Conversely, when no stimulus could appear to its right or left, only an eccentricity effect was found, i.e., RTs to central stimuli were faster than RTs to right or left stimuli (Experiment 2).

GENERAL DISCUSSION

There are two main streams that address human neglect as a disorder of attention and they are based on two models, respectively suggested by Heilman and his associates (Heilman *et al.*, 1987) and Kinsbourne (1987). Heilman *et al.* (1987) proposed a dichotomous hemispace model, according to which each side of the brain contains its own activating system and subserves orienting responses to the opposite half space. However, in order to explain the fact that neglect occurs more frequently following right than left hemisphere lesions (Ogden, 1987), they further assumed that the attentional

mechanism located in the right hemisphere subserves the whole egocentric space, whereas the left is only related to the opposite (right) half (Heilman *et al.*, 1985). Thus the effect of a left hemisphere lesion on orienting can be compensated for by the right hemisphere, whereas a right hemisphere lesion limits orienting response to the right space. In contrast, Kinsbourne (1987) proposed that neglect is a directional and not a hemisphere phenomenon. Basic to this model is the assumption that two antagonistic vectors direct attention to the two opposite sides of egocentric space. Damage to one hemisphere impairs the contralaterally oriented vector and unbalances the attentional system in favour of shifts contraversive to the intact side because it releases the competitor vector from inhibition. In order to explain the greater incidence of neglect after a right rather than a left hemispheric lesion, Kinsbourne proposed that right and left directional tendencies in humans, though opposite, are not equal. More precisely, he proposed that the left brain activation powerfully generates rightward turning, whereas the leftward turning generated by the right hemisphere is weak.

According to Heilman's model the lateral attentional differences can exist only between the two half-fields and this is in contrast to the results of the present experiment, as well as with recent evidence where it was shown that the attentional imbalance is not merely restricted to one hemisphere, but also affects two separate points on the left-right dimension whatever the absolute location of these points on that dimension (Corin and Bender, 1972; Kinsbourne, 1977; Altman *et al.*, 1979; Lamotte and Acuña, 1978; Bisiach *et al.*, 1984; Lâdavas, 1987; Posner *et al.*, 1987; Lâdavas *et al.*, 1989).

The attentional imbalance within the hemifield ipsilateral to the lesion is predicted by Kinsbourne's model. When the right hemisphere is inactivated by the lesion, the left oriented vector is impaired and therefore releases the right oriented vector from the inhibition. As a consequence, attention swings sharply rightward in the egocentric space and the increased attention to the right is accompanied by a decreased attention to the left. This model fits very well with the results of the present study for two main reasons. First, by postulating two antagonistic vectors which direct attention to the two opposite sides of egocentric space, it explains why the attentional imbalance found in the present study is related to the relative positions of the 3 stimuli on the left-right dimension and not to their retinal positions. Secondly, this model predicts the attentional bias found in the present study for the ipsilesional stimuli. When the patients had to respond to 3 spatial locations aligned horizontally, the speed and accuracy of response to the right stimulus were the same as when they had to focus attention on it. These results prove that in Experiment 1 the focus of attention was not on a point halfway between the 2 stimuli, as in normal subjects, but on the right stimulus. As a consequence of the increased attention to the right there is a gradually decreasing attention to the left so that responses to the central stimulus were faster than responses to the right stimulus and shorter than responses to the left stimulus.

As we noted before, in patients with a right parietal lesion, the orienting response is under the control of the intact left hemisphere and, therefore, the essential element which characterizes the preparation to respond to visual stimuli is the specification of the direction 'right' as opposed to 'left'. When a patient has to respond to the stimulus which occupies a right position, the task does not require any correction of the directional program, because the system is already prepared to respond to that direction. Conversely, if the subject has to respond to the left stimulus, the task requires the correction of the

directional bias concerning the spatial position of stimuli, and as a result the emission of response is retarded or omitted, hence the cost for RT and the errors consistently found for left stimuli. This interpretation of course implies that reorienting of attention is necessary before a manual response can be emitted to a stimulus that appears in a left unattended position. Posner (1980, 1982) has suggested that an arbitrary response, that is one not automatically triggered by the stimulus, only occurs through the commitment of conscious attention. In other words, a stimulus must enter the focus of attention and become conscious before an arbitrary response to it can be emitted. For patients with right parietal lesions a left stimulus is not aligned with the focus of attention which is displaced to the rightmost stimulus and therefore the increase in RT at left positions can be regarded as a measure of the cost imposed by the initial misalignment of the attentional focus and the resulting necessity to redirect it before responding (Posner *et al.*, 1978; Posner, 1980). If the misalignment of the attentional focus does not occur, the response is omitted, even though the stimulus can influence the patient's behaviour without the patient being aware of the stimulus (Volpe *et al.*, 1979; Marshall and Halligan, 1988).

In conclusion, the results of the present experiments can be explained by the directional attentional model proposed by Kinsbourne, with the exception of the reduced responsivity found for LVF stimuli. Kinsbourne's model implies that the right-left attentional gradient is continuous across the whole field so that costs should increase as a function of the distance of the target from the attended position. This prediction was not supported in the present experiments because the results showed a discontinuity of this right-left attentional gradient at the junction of left and right hemispace. A larger cost was paid when the stimuli were presented at nonattended locations in the hemifield contralateral to the lesion. This larger cost can be explained by considering the deficit shown by patients with right hemisphere lesions in maintaining a high level of alertness. It is possible that this difficulty becomes particularly evident for stimuli presented in the visual field directly connected with it. If this interpretation is correct, we should expect a reduced responsivity to LVF stimuli after a right hemisphere lesion, independent of the loci of the lesion within this hemisphere. A recent study by Petersen *et al.* (1989) seems to show that this is the case. Using the cueing paradigm, they showed that lesions in frontal and temporal areas produce a generalized decrement of reaction times and an additional decrement for all targets presented in the contralesional field. However, these data are only partially confirmed by the study of Ladavas *et al.* (1989), where an overall decrement of reactions times in patients with right temporal lesions was shown, but no significant difference between the two visual fields. Therefore, the greater attentional cost in LVF found in Experiment 1 as well as in Experiment 2 requires further investigation in order to be clarified.

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THE RELATIONSHIP BETWEEN LOCOMOTOR DISABILITY, AUTONOMIC DYSFUNCTION, AND THE INTEGRITY OF THE STRIATAL DOPAMINERGIC SYSTEM IN PATIENTS WITH MULTIPLE SYSTEM ATROPHY, PURE AUTONOMIC FAILURE, AND PARKINSON'S DISEASE, STUDIED WITH PET

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SUMMARY

¹⁸F-dopa and S-¹¹C-nomifensine (NMF) are positron emitting tracers whose caudate and putamen uptake reflects striatal dopamine storage capacity and the integrity of dopamine reuptake sites, respectively. Using these two tracers, the integrity of the presynaptic striatal dopaminergic system has been studied with positron emission tomography (PET) in 10 subjects with multiple system atrophy (MSA, Shy-Drager syndrome) who had an akinetic-rigid syndrome that was poorly responsive to L-dopa, autonomic failure, and cerebellar ataxia. PET findings for the 10 MSA patients were compared with those for 13 age-matched controls, 8 subjects with L-dopa responsive Parkinson's disease (PD), and 7 subjects with pure autonomic failure (PAF).

Influx constants, K_i , reflecting specific ¹⁸F-dopa uptake into striatal tissue, were severely reduced in the putamen and caudate of the 10 MSA subjects (mean putamen K_i 0.005 min⁻¹ MSA vs 0.013 min⁻¹ controls; mean caudate K_i 0.007 min⁻¹ MSA vs 0.013 min⁻¹ controls). Reduction of putamen, but not caudate, ¹⁸F-dopa uptake correlated with severity and duration of locomotor disability. Eight patients with PD, and a similar degree and duration of locomotor disability to the patients with MSA, demonstrated equal impairment of mean putamen ¹⁸F-dopa uptake, but significant preservation of mean caudate function. The 7 PAF patients had normal mean levels of putamen and caudate ¹⁸F-dopa uptake, although 1 individual PAF patient had significantly impaired striatal function.

The MSA and PD groups of subjects both showed significantly reduced levels of specific striatal S-¹¹C-NMF binding, again caudate function being relatively preserved in PD. It is concluded that in both MSA and PD there is a parallel decline of striatal dopamine storage capacity and reuptake site integrity, probably reflecting a loss of nigrostriatal nerve terminals. Caudate function is relatively preserved in PD compared with MSA. The majority of PAF patients have an intact nigrostriatal dopaminergic system, suggesting that PAF is a condition distinct from PD and MSA in spite of some pathological similarities. PET is capable of detecting subclinical nigrostriatal involvement in PAF patients when this is present.

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INTRODUCTION

Multiple system atrophy (MSA) is a condition characterized clinically by variable combinations of parkinsonism (extrapyramidal rigidity, bradykinesia, tremor) which is poorly responsive to L-dopa, autonomic failure, and cerebellar ataxia (Quinn, 1989). It includes conditions such as striatonigral and olivopontocerebellar degeneration in its spectrum. When parkinsonism and autonomic failure predominate, the condition has been referred to as the Shy-Drager syndrome (Shy and Drager, 1960). Postmortem findings reveal neuronal loss from the basal ganglia, pigmented brainstem nuclei, dentate nuclei, and intermediolateral columns of the spinal cord, in the absence of Lewy bodies or neurofibrillary tangles (Bannister and Oppenheimer, 1972; Spokes *et al.*, 1979). This pathology distinguishes MSA from Parkinson's disease (PD), the Steele-Richardson-Olszewski syndrome, and postencephalitic parkinsonism, PD being associated with Lewy body degeneration of the pigmented brainstem nuclei, while the other two conditions are associated with neurofibrillary tangle formation in brainstem nuclei (Bethlem and den Hartog Jager, 1960; Steele *et al.*, 1964). Both PD and MSA are characterized by a profound loss of striatal dopamine, but while striatal choline acetyl transferase (CAT) and glutamic acid decarboxylase (GAD) levels are normal in PD (Javoy-Agid *et al.*, 1986), striatal CAT and GAD levels are depleted in MSA (Spokes *et al.*, 1979).

Although PD is pathologically quite distinct from MSA, it can be difficult at times to distinguish these two conditions clinically. Both PD and MSA are associated with an akinetic-rigid syndrome and autonomic failure. PD patients are generally more L-dopa responsive, and have more prominent rest tremor than MSA patients. They less commonly have autonomic failure. It has been estimated that between 5 and 11% of cases diagnosed as having PD on clinical grounds alone actually turn out to have MSA at autopsy (Takei and Mirra, 1973; Duvoisin, 1984; Quinn, 1989). It would clearly be advantageous to have additional means of distinguishing the various akinetic-rigid syndromes, given the diagnostic difficulties that can arise from clinical assessment alone.

Pure autonomic failure (PAF) is a condition characterized by orthostatic hypotension, impaired cardiovascular reflexes, anhidrosis, impotence, and urinary dysfunction (Bannister and Oppenheimer, 1972). It tends to present later than PD and MSA, and unlike these two conditions is not associated with extrapyramidal rigidity or other neurological signs. Those few PAF subjects who have come to autopsy have shown cell loss in the intermediolateral columns of the spinal cord similar to that found in MSA patients. Lewy bodies were also found in their sympathetic ganglia and substantia nigra (Johnson *et al.*, 1966; Vanderhaeghen *et al.*, 1970; Bannister and Oppenheimer, 1972). Such pathology can also be seen in PD subjects with autonomic failure, although cell loss from the substantia nigra is far greater. This raises the question as to whether PAF and PD are extremes of an overlap syndrome, both involving the presence of Lewy bodies in pigmented brainstem nuclei and atrophy of the intermediolateral column cells of the spinal cord, or whether they are distinct conditions with superficially similar pathology.

Positron emission tomography (PET) provides a means of studying regional cerebral function in man, and is ideally suited for investigating the integrity of the striatal (caudate and putamen) dopaminergic system in patients with movement disorders. ^{18}F -6-fluorodopa (^{18}F -dopa) is a positron emitting tracer which, when administered intravenously,

is taken up by the nigrostriatal nerve terminals in the caudate and putamen and stored as ^{18}F -dopamine and its metabolites (Firnau *et al.*, 1987). Garnett *et al.* (1984) have shown that in early (Hoehn and Yahr, stages 1 and 2) PD the uptake of ^{18}F -dopa is impaired in the putamen but normal in the caudate. S- ^{11}C -nomifensine (^{11}C -NMF) is a positron emitting tracer which binds to dopamine reuptake sites on the nigrostriatal nerve terminals in caudate and putamen, and noradrenaline reuptake sites in the thalamus (Scatton *et al.*, 1985). The R-isomer is inactive. A preliminary PET study, using a racemic mixture of R and S- ^{11}C -NMF, has reported a decrease of striatal dopamine reuptake sites in 3 out of 6 PD patients studied (Tedroff *et al.*, 1988). Racemic R,S- ^{11}C -NMF gives a low specific signal, however, making differences in striatal tracer uptake between normal subjects and PD patients difficult to detect.

The purpose of our study was to examine the integrity of the presynaptic dopaminergic system in MSA, PAF, and PD patients by measuring their striatal uptake of ^{18}F -Dopa and S- ^{11}C -NMF with PET. Our intention was to determine whether MSA and PD patients show different patterns of disruption of striatal function, and to correlate any impairment in the function of the caudate and putamen with the degree of locomotor disability. We were also interested to see whether evidence of subclinical nigrostriatal damage could be found in PAF subjects, in view of the reported presence of Lewy bodies in the substantia nigra in this condition. In this way we hoped to be able to predict which PAF subjects are potentially at risk of developing an extrapyramidal syndrome.

METHODS

Patient selection

Ten MSA patients, aged 40–73 yrs, were PET scanned. All had an akinetic-rigid syndrome associated with severe impairment of cardiovascular reflexes and other symptoms of autonomic failure. Seven of the 10 had cerebellar ataxia and 6 had cerebellar and/or brainstem atrophy on CT and/or MRI brain scan. Clinical disease duration ranged from 1–12 yrs, and locomotor disability from 2–5 on the Hoehn and Yahr scale (Hoehn and Yahr, 1967). Clinical details of the MSA patients are presented in Table 1. Four out of the 10 showed little or no response to L-dopa; the other 6 presented with profound orthostatic hypotension and were consequently not treated with dopamine agonists. None of the 10 MSA patients studied had taken L-dopa or dopamine agonists for a minimum of 6 months before PET. Seven PAF patients, aged 56–78 yrs, also underwent PET. All had severe orthostatic hypotension and impaired cardiovascular reflexes, plus variable degrees of urinary dysfunction, constipation, impotence, and anhidrosis. Disease duration ranged from 1–12 yrs. Their clinical details are shown in Table 2. None of the PAF patients had clinical evidence of extrapyramidal dysfunction or other neurological signs, and all had normal somatic nerve conduction studies.

PET findings for the above patients were compared with those of 13 age-matched control subjects (40–78 yrs) who had no neurological abnormalities on clinical examination. Two additional normal studies were rejected as outliers, 1 showing bilateral caudate ^{18}F -dopa uptake, and another left putamen ^{18}F -dopa uptake, reduced to more than 3 SDs below the normal mean. Eight age-matched PD patients (50–73 yrs) with locomotor disability ranging from 2–4 on the Hoehn and Yahr scale were also studied. All the PD patients showed a good response to L-dopa, and were taking 400 mg–1.5 g daily at the time of PET. Patient details are shown in Table 3. Their medication was stopped for at least 12 h prior to PET.

All subjects were fasted for 12 h before PET to minimize endogenous levels of plasma aminoacids. Informed consent was obtained from all subjects before they were scanned. These studies were approved by the Ethics Committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London, and the Administration of Radioactive Substances Advisory Committee, UK.

TABLE 1 CLINICAL DETAILS OF THE MULTIPLE SYSTEM ATROPHY PATIENTS

Case	Sex	Age (yrs)	Duration of symptoms (yrs)		H and Y score	Cerebellar ataxia	L-dopa response	MRI/CT scan
			(EP)	(AF)				
1 (C.B.)	F	53	4	6	3	Y	NT	—
2 (R.G.)	M	67	10	10	5	Y	NT	CBA
3 (D.P.)	F	40	3	3	3	N	Poor	Nor
4 (E.R.)	F	73	3	8	5	Y	NT	BA
5 (J.R.)	M	64	1	4	2	N	Poor	CA
6 (M.F.)	F	55	6	2	4	Y	NT	CBA
7 (E.D.)	M	53	2	12	4	Y	NT	BA
8 (R.K.)	M	58	3	3	3	Y	None	Nor
9 (H.B.)	M	67	2	10	3	Y	NT	CA
10 (D.C.)	M	61	10	4	4	N	None	Nor

EP = extrapyramidal; AF = autonomic failure; H and Y = Hoehn and Yahr scale; NT = not tested because of severe orthostatic hypotension; CA/CBA/BA = cerebellar and/or brainstem atrophy, Nor = normal.

TABLE 2 CLINICAL DETAILS OF THE PURE AUTONOMIC FAILURE PATIENTS

Case	Sex	Age (yrs)	Duration (yrs)	Symptoms
11 (A.H.)	F	61	8	OH, Anh, UF
12 (E.H.)	F	60	12	OH, Anh, UR
13 (D.S.)	F	67	11	OH, Anh, UF
14 (H.C.)	M	63	7	OH, Imp, UF
15 (G.L.)	M	56	10	OH, Anh, Imp
16 (M.T.)	F	78	1	OH, Anh, Noct
17 (M.F.)	F	75	9	OH, Noct

OH = orthostatic hypotension and impaired cardiovascular reflexes, Anh = anhidrosis, UF = urinary frequency; Imp = impotence, UR = urinary retention; Noct = nocturia

TABLE 3. CLINICAL DETAILS OF THE PARKINSON'S DISEASE PATIENTS

Case	Sex	Age (yrs)	Duration (yrs)	H, Y score	Treatment
18 (S.D.)	M	63	10	3	Sinemet-275 3×daily Sinemet-110 2×daily Amantadine 100 mg 2×daily
19 (A.G.)	M	73	30	4	Sinemet-110 12×daily Sinemet-275 1×daily Amantadine 100 mg 3×daily
20 (P.C.)	M	63	15	3	Sinemet-110 6×daily Benzhexol 2 mg 3×daily
21 (R.D.)	M	59	4	2	Madgar-250 5×daily
22 (S.W.)	M	55	3	2	Sinemet-275 4×daily
23 (H.T.)	F	64	7	3	Benzhexol 5 mg 3×daily
24 (V.K.)	M	70	6	4	Madopar-250 1×daily Madopar-125 7×daily Selegiline 10 mg daily
25 (W.J.)	M	62	10	3	Sinemet-110 7×daily

Scanning procedure

^{18}F -dopa. All subjects were premedicated 1 h before PET scanning with an oral dose of 100 mg of carbidopa, a peripheral dopa decarboxylase antagonist. Between 3 and 5 mCi of ^{18}F -dopa, specific activity 8.3 ± 2.2 mBq/ μmol , prepared according to the method of Adam *et al.*, 1986, were infused intravenously in 10 ml of normal saline over 2 min using a Harvard pump. At the onset of tracer infusion, PET was commenced using an ECAT 938-08/12 tomograph (CTI Knoxville, Tennessee, USA) yielding 15 simultaneous axial tomographic slices with a full-width-half-maximum resolution of $7\text{ mm} \times 7\text{ mm} \times 8\text{ mm}$ (Spinks *et al.*, 1988). Serial scans were performed initially at 1 min, extending to 5 min intervals, yielding a total of 24 time frames over 90 min. Emission scans were corrected for tissue attenuation of 511 keV γ radiation using measured transmission data obtained with an external ^{68}Ge ring source, as previously described (Frackowiak *et al.*, 1980).

S - ^{11}C -NMF. 6–10 mCi of tracer, specific activity 8600 ± 3400 mBq/ μmol , prepared according to the method of Uhlin *et al.* (1989), were infused intravenously in 5 ml of normal saline over 2 min using a Harvard pump. At the onset of tracer infusion, PET was commenced, serial scans being performed initially at 30 s, extending to 5 min intervals, yielding a total of 21 time frames over 60 min.

Data analysis

^{18}F -dopa uptake was analysed using the multiple-time graphical analysis (MTGA) approach developed by Patlak and Blasberg (1985) with a nonspecific occipital reference tissue input function in preference to plasma. At 30 min after ^{18}F -dopa administration, ^{18}F radioactivity in nonspecific brain regions reaches equilibrium with arterial plasma (Leenders *et al.*, 1986; Martin *et al.*, 1989). MTGA plots of the ratio of both nonspecific occipital:plasma, and cerebellar:plasma, ^{18}F activity versus the transformed and expanded time scale integrated plasma/plasma ^{18}F activity become flat after 30 min of real time (*see* fig. 1A). Our 13 normal subjects gave mean occipital and cerebellar gradients of $2.9 \times 10^{-4} \pm 3.9 \times 10^{-4} \cdot \text{min}^{-1}$, and $3.7 \times 10^{-4} \pm 4.3 \times 10^{-4} \cdot \text{min}^{-1}$, respectively, neither of which was significantly different from zero. From 30 to 90 min following ^{18}F -dopa administration specific ^{18}F uptake in striatum continuously increases, the ^{18}F activity being primarily in the form of ^{18}F -dopamine (Firnau *et al.*, 1987). ^{18}F is subsequently released as the ^{18}F dopamine metabolites ^{18}F -homovanillic acid and ^{18}F -dopac. MTGA plots of striatal:plasma ^{18}F activity versus integrated plasma/plasma ^{18}F activity linearly increase between 30 and 90 min of real time (*see* fig. 1A).

MTGA plots of striatal:occipital ^{18}F uptake vs the transformed and expanded time scale integrated occipital/occipital ^{18}F activity are also linear between 30 and 90 min of real time (*see* fig. 1B). Linear

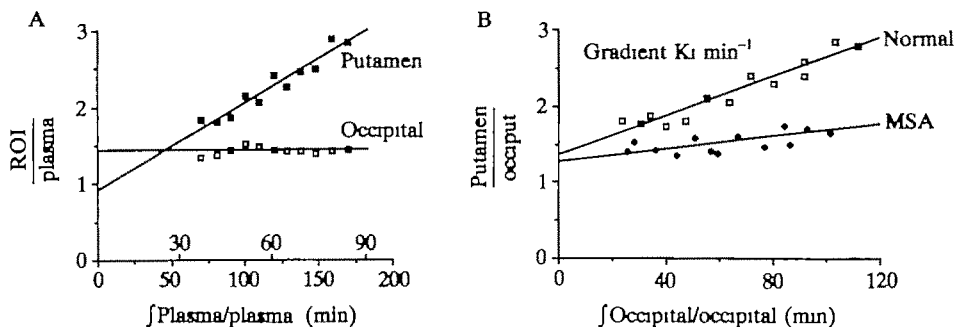


FIG. 1 A, Multiple time graphic analysis (MTGA) plots of regional cerebral:plasma ^{18}F activity vs a real time scale and an expanded transformed time scale (integrated plasma/plasma ^{18}F activity) of a normal subject. The occipital curve is flat, indicating that no specific irreversible ^{18}F accumulation is occurring, while the putamen shows linearly increasing specific irreversible ^{18}F uptake. B, MTGA plots of putamen ^{18}F uptake for a normal subject and MSA patient using a nonspecific occipital input function. The gradients of these plots represent influx constants, K_i , which reflect specific putamen ^{18}F accumulation.

fits of putamen/occipital MTGA plots for our 13 normal controls yielded a mean correlation coefficient of 0.94 ± 0.04 . In 6 out of the 13 controls proceeding to higher polynomial or multiexponential fits led to no significant improvement in the fit as judged by the *F* statistic. In the other 7 controls, improved fits could be obtained, but not with any consistent function. This suggested that the improvement in the fit was a reflection of noise in the data, rather than deviation from nonlinearity. The gradients of such MTGA plots can be regarded as influx constants, K_i , which reflect specific striatal ^{18}F accumulation (Patlak and Blasberg, 1985). These K_i values are a composite measure of the rate of striatal ^{18}F -dopa uptake, dopa decarboxylase activity, and the rate of ^{18}F -dopa metabolism. We used an occipital, rather than cerebellar, nonspecific reference input function in our studies as MSA is associated with cerebellar atrophy. In our 13 normal subjects occipital and cerebellar nonspecific input functions gave very similar K_i values for striatal ^{18}F -dopa uptake.

^{11}C -NMF uptake was analysed by measuring the average ratio of striatal:occipital tracer activity between 30 and 50 min (see fig. 2A). The difference in ^{11}C -NMF uptake in striatum and nonspecific brain regions becomes constant after 25 min (see fig. 2B), and so this ratio approach provides a simple measure of striatal dopamine reuptake site integrity (Tedroff *et al.*, 1988).

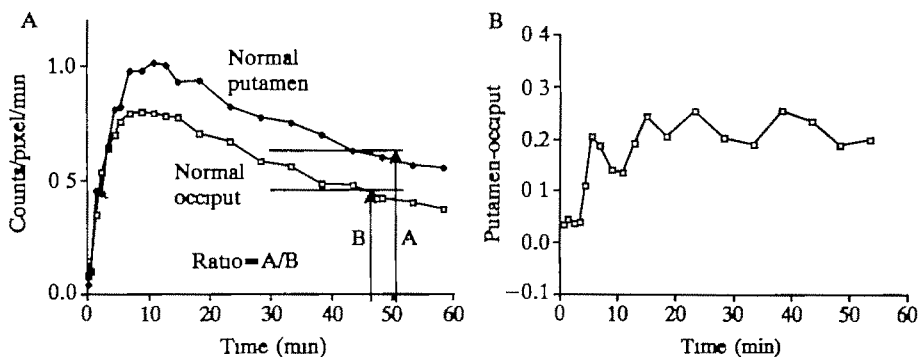


FIG. 2. A, plot of regional cerebral ^{11}C -NMF uptake against time. After 25 min the difference in ^{11}C uptake by striatal and occipital regions becomes constant and the ratio of mean striatal:occipital activity (A/B) over 30–55 min reflects specific striatal ^{11}C -NMF uptake. B, plot of striatal minus occipital ^{11}C -NMF uptake against time for a normal subject. The difference curve plateaus after 25 min.

Regions of interest (ROIs) were placed on single optimum planes and sized either by direct inspection of PET images in the case of normal subjects, or by superimposing CT or MRI images at the same axial level on the PET images of patients. Tracer activity in the heads of the caudate nuclei was sampled using 1 cm diameter circular ROIs, while putamen activity was sampled with 0.8×2.4 cm diameter elliptical ROIs set along the long axis of the nuclei. Average caudate and putamen tracer uptake was then computed and plotted as a function of time. Thalamic tracer uptake was sampled using two 1.2 cm diameter circular ROIs, while occipital and cerebellar tracer concentrations were sampled using 4×9 cm diameter elliptical ROIs. Data calculation was performed on Apple Mac II personal computers. Statistical comparisons were performed using two-tailed Student's *t* tests with Bonferroni's correction for multiple comparisons.

RESULTS

Fig. 3 shows PET images of striatal ^{18}F uptake, 60–90 min after intravenous ^{18}F -dopa administration, for a normal subject and an MSA patient. Tracer accumulation is impaired in both caudate and putamen in the MSA scans. Fig. 4A gives details of individual striatal ^{18}F -dopa influx constants, K_i , for age-matched normal subjects, and patients with PAF and MSA. Both the putamen and caudate mean K_i values were

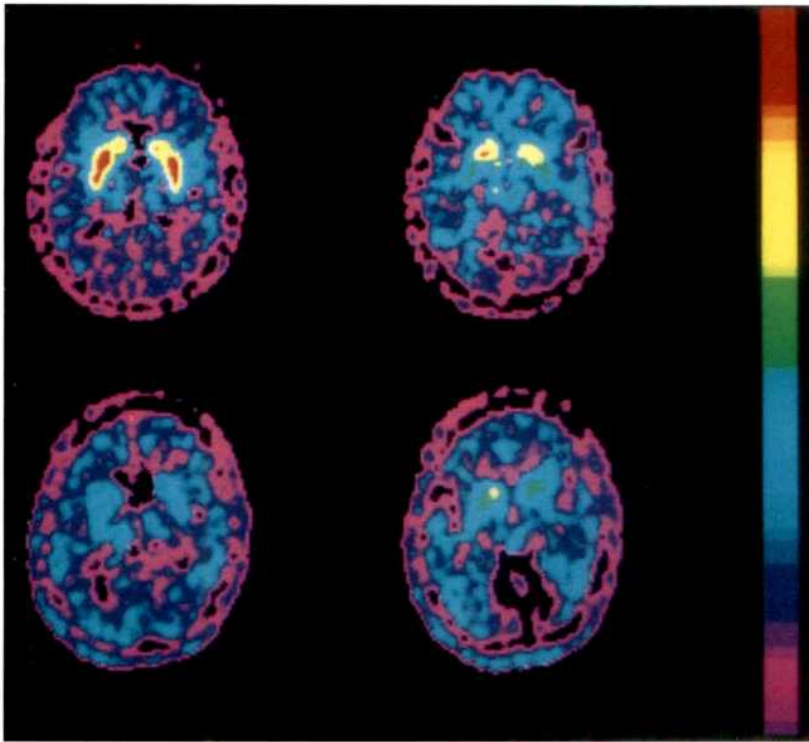


FIG. 3. PET scans of ^{18}F -dopa uptake 60–90 min following intravenous tracer administration for a normal subject (top) and MSA patient (bottom). The upper normal images show high ^{18}F signal in putamen and head of caudate nuclei. The MSA images show severely reduced ^{18}F signal in both putamen and caudate.

significantly depressed in MSA, uptake being more affected in the putamen (*see* Table 4). Mean striatal K_i values were normal in the 7 patients with PAF, although 1 of the PAF patients (Case 14) had levels of ^{18}F -dopa uptake into both putamen and caudate that were reduced by more than 2.5 SDs below the normal mean.

Fig. 5A shows that there was a significant inverse correlation ($P < 0.05$) between individual influx constants for ^{18}F -dopa uptake into putamen and the degree of locomotor disability on the Hoehn and Yahr scale for the 10 MSA subjects, none of whom was currently taking L-dopa therapy. Individual MSA putamen K_i values also showed an inverse correlation ($P < 0.01$) with duration of locomotor disability (fig. 6A). No inverse correlation was observed between K_i for caudate ^{18}F -dopa uptake and motor disability (fig. 5B), nor for putamen or caudate ^{18}F -dopa uptake and the clinical duration of autonomic dysfunction (fig. 6B).

Fig. 4B compares individual striatal K_i values of ^{18}F -dopa uptake for the 13 normal subjects, 10 MSA, and 8 L-dopa responsive PD patients. ^{18}F -dopa uptake into putamen was equally severely depressed in the MSA and PD patients, but there was a significant preservation of caudate function in PD relative to MSA ($P < 0.01$, Student's *t* test). Values of mean striatal ^{18}F -dopa K_i values for the normal, MSA, PAF, and PD groups of subjects are detailed in Table 4.

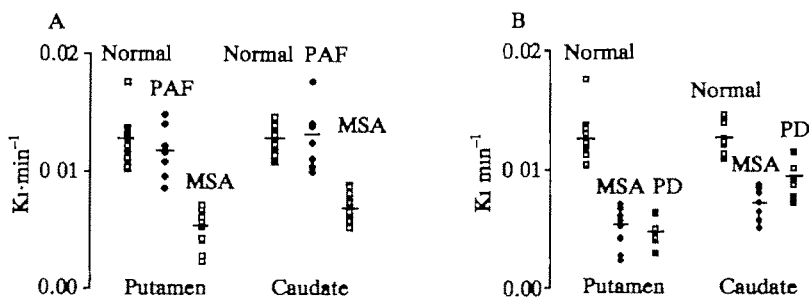


FIG. 4. A, dot diagram showing individual striatal ^{18}F -dopa influx constants for 13 normal subjects, 7 PAF, and 10 MSA patients. Mean MSA putamen and caudate K_i values are significantly reduced (see Table 4). B, dot diagram showing individual striatal ^{18}F -dopa influx constants for 13 normal subjects, 10 MSA, and 8 PD patients. Mean putamen and caudate K_i values are significantly reduced in both MSA and PD. Mean MSA caudate K_i values are significantly more affected than PD (see Table 4).

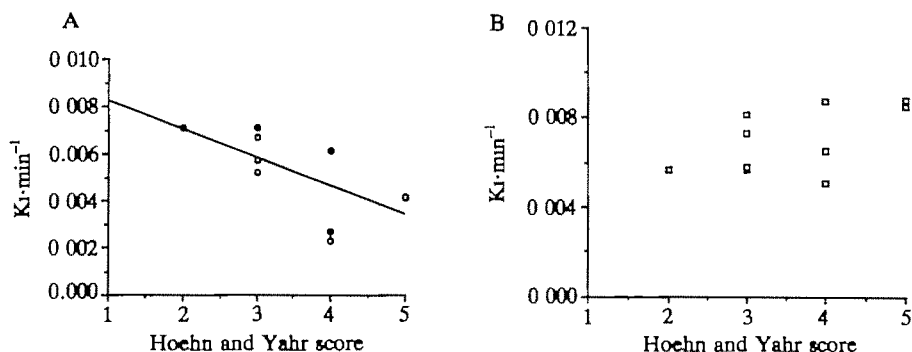


FIG. 5. A, plot of individual putamen ^{18}F -dopa influx constants vs Hoehn and Yahr disability scores for 10 MSA patients. A significant negative correlation is seen ($r = 0.67$, $P < 0.05$). B, similar plot to A but with caudate ^{18}F -dopa influx constants. No significant negative correlation is present.

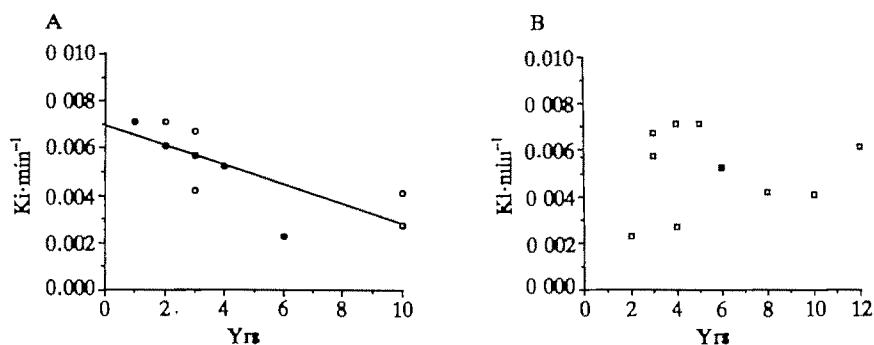


FIG. 6. A, plot of individual putamen ^{18}F -dopa influx constants vs duration of locomotor disability for the 10 MSA patients. A significant negative correlation is present ($r = 0.78$, $P < 0.01$). B, similar plot to A, but vs duration of autonomic failure. No significant negative correlation is present.

TABLE 4. MEAN STRIATAL ^{18}F -DOPA INFLUX CONSTANTS (K_i^{-1}) IN MSA, PD AND PAF

	Putamen (mean $\pm$ SD)	Caudate (mean $\pm$ SD)	Putamen/caudate (mean $\pm$ SD)
Normals (13)	0.0125 $\pm$ 0.0019	0.0125 $\pm$ 0.0013	1.01 $\pm$ 0.12
PAF (7)	0.0117 $\pm$ 0.0023	0.0128 $\pm$ 0.0027	0.93 $\pm$ 0.15
MSA (10)	0.0051 $\pm$ 0.0017*	0.0070 $\pm$ 0.0014***	0.75 $\pm$ 0.29*
PD (8)	0.0047 $\pm$ 0.0012*	0.0091 $\pm$ 0.0013***	0.52 $\pm$ 0.18*

* $P < 0.05$ Bonferroni statistics compared with normals. **PD caudate vs MSA caudate
 $P < 0.01$ (Student's t test).

Fig. 7 shows PET images of striatal and thalamic S- ^{11}C -NMF uptake for a normal subject and an MSA patient. While striatal ^{11}C -NMF uptake is severely depressed in the MSA subject, thalamic tracer uptake remains normal, suggesting that striatal dopamine reuptake sites, but not thalamic catecholamine reuptake sites, are diminished in MSA. Table 5 shows mean striatal:occipital, and thalamic:occipital uptake ratios of ^{11}C -NMF measured over 30–50 min following tracer administration for normal, PAF, MSA, and PD groups of subjects. Again, ^{11}C -NMF uptake into putamen was severely depressed in both MSA and PD patients. Caudate function was also significantly depressed in both groups of patients, but there was relative sparing of caudate function in PD.

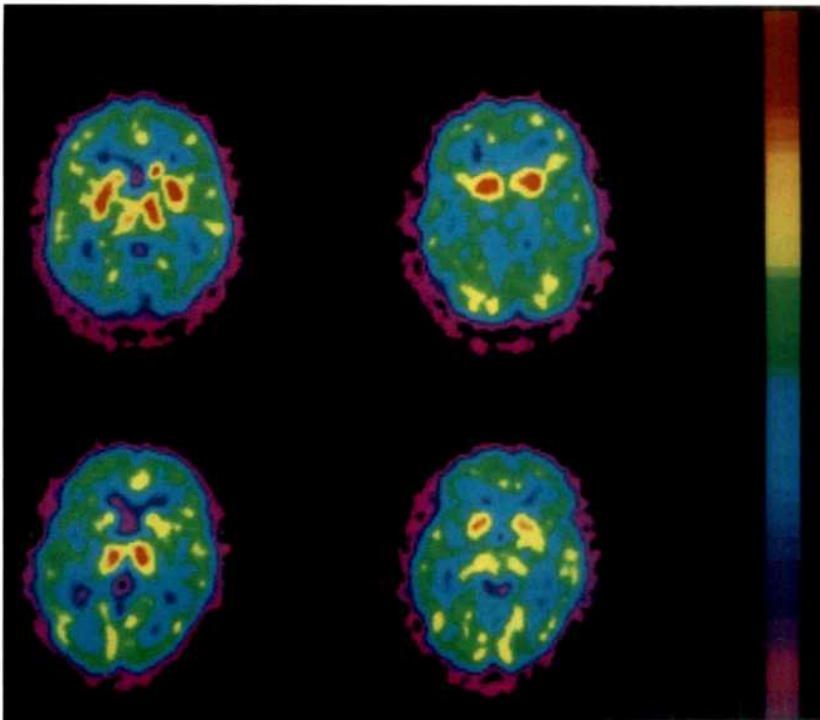


FIG. 7. PET scans of S- ^{11}C -NMF uptake, integrated over the 60 min of scanning, for a normal subject (top) shows high specific ^{11}C signal in thalamus, putamen, and heads of caudate nuclei. The MSA images (bottom) show high thalamus, but reduced specific striatum ^{11}C signals.

TABLE 5 MEAN STRIATAL/THALAMIC OCCIPITAL RATIOS (30-50 MIN) FOR S-¹¹C-NMF UPTAKE IN MSA, PD AND PAF

	Putamen (mean $\pm$ SD)	Caudate (mean $\pm$ SD)	Thalamus (mean $\pm$ SD)
Normals (6)	1.98 $\pm$ 0.12	1.85 $\pm$ 0.15	1.32 $\pm$ 0.07
PAF (1)	2.04	1.92	1.46
MSA (7)	1.34 $\pm$ 0.10*	1.35 $\pm$ 0.30*	1.26 $\pm$ 0.11
PD (8)	1.38 $\pm$ 0.11*	1.48 $\pm$ 0.19*	1.31 $\pm$ 0.14

* $P < 0.05$ Bonferroni statistics compared with normals.

DISCUSSION

Our findings demonstrate that both ¹⁸F-dopa and S-¹¹C-NMF are useful PET tracers for measuring the functional integrity of the nigrostriatal dopaminergic neurons in man. ¹⁸F-dopa is rapidly converted to ¹⁸F-dopamine by dopa decarboxylase in the striatum, and then more slowly to ¹⁸F-homovanillic acid (HVA) and ¹⁸F-dihydroxyphenylacetic acid (Firnau *et al.*, 1987). In plasma, in the presence of 100 mg of carbidopa, 6-¹⁸F-dopa is progressively metabolized to 3-O-methyl-6-¹⁸F-L-dopa (Hoffman *et al.*, 1989). Like ¹⁸F-dopa, the 3-O-methyl metabolite is transported passively across the blood-brain barrier by the neutral amino acid carrier and then equilibrates throughout all brain regions (Martin *et al.*, 1989). As a consequence of the formation of these various ¹⁸F-dopa metabolites in striatum and plasma, it is difficult to apply simple compartmental modelling to the kinetics of striatal ¹⁸F accumulation following intravenous ¹⁸F-dopa infusion.

The multiple time graphical analysis (MTGA) approach developed by Patlak and Blasberg (1985) provides an alternative means of examining striatal ¹⁸F-dopa uptake. Essentially, if a substrate is taken up irreversibly from plasma into a specific cerebral compartment, then after a finite time t' $A_{sp}(t)/Cp(t)$ becomes a linear function of $\int Cp(t)/Cp(t)$ where $A_{sp}(t)$ and $Cp(t)$ are the concentrations of substrate in the specific brain compartment and plasma at time t . If the substrate comes to equilibrium in other nonspecific or reference areas of brain by time t' then $A_{sp}(t)/A_{ref}(t)$ is also a linear function of $\int A_{ref}(t)/A_{ref}(t)$ after time t' . The gradient of such a plot gives an influx constant $K_i \text{ min}^{-1}$ which reflects the specific uptake and storage rate of the substrate. Strictly our ¹⁸F-dopa uptake kinetics into striatum do not fulfill Patlak-Blasberg criteria. Firstly, ¹⁸F activity is not irreversibly trapped in striatum. Secondly, ¹⁸F-dopa is metabolized to 3-O-methyl-F-dopa in plasma which is transported with ¹⁸F-dopa across the blood-brain barrier and equilibrates throughout the brain (Martin *et al.*, 1989). Having said that, this simple MTGA approach yields linear plots when ¹⁸F-dopa uptake into striatum is followed between 30 and 90 min after its intravenous administration, both with an occipital and a cerebellar input function. This linearity probably reflects the fact that ¹⁸F activity is effectively trapped in striatum as ¹⁸F-dopamine during this time period (Firnau *et al.*, 1987). The presence of 3-O-methyl-¹⁸F-dopa will have a constant background effect on the $A_{sp}(t)/A_{ref}(t)$ y axis, and act to contract the $A_{ref}(t)/A_{ref}(t)$ axis. As a consequence, K_i values derived from our MTGA plots may be overestimates of the K_i values that would be obtained in the absence of the methyl metabolite.

In spite of the above drawbacks, this simple MTGA approach provides a reasonable

way of comparing regional putamen and caudate dopaminergic function in groups of patients with different akinetic-rigid syndromes. Boyes *et al.* (1986) have shown that levels of the plasma 3-O-methyl- ^{18}F -dopa metabolite are similar in age-matched normals and PD patients, and this is also likely to be the case for MSA patients. The K_i values derived are composite rate constants, comprising the summed effects of rate constants describing striatal ^{18}F -dopa uptake, ^{18}F -dopamine formation, and storage. Unfortunately, the MTGA approach does not allow the determination of rates of endogenous dopamine production or turnover in the striatum because of lack of information as to the size of the natural precursor pools.

The kinetics of S- ^{11}C -NMF uptake by the striatum also pose a complex modelling problem. In plasma, ^{11}C -NMF is conjugated within minutes to form a glucuronide, and is more slowly metabolized to hydroxylated and methoxylated forms which are also rapidly conjugated (Heptner *et al.*, 1984). Again simple compartmental modelling does not adequately describe the kinetics of uptake of this tracer from plasma into the striatum. The difference in ^{11}C -NMF uptake by the striatum compared with brain regions poor in catecholamine reuptake sites, such as the occipital and cerebellar areas, becomes constant after 25 min (fig. 2B). Tedroff *et al.* (1988) have used striatal:cerebellar ^{11}C -NMF uptake ratios at 40 min after administration of the tracer to provide a simple estimation of the integrity of striatal dopamine reuptake sites. Our data illustrate that striatal:occipital ^{11}C -NMF uptake ratios measured 30–50 min after ^{11}C -NMF administration can be used in a similar fashion. Table 5 shows that approximately 50% of the striatal ^{11}C -NMF signal represents specific tracer binding when this ratio approach is used.

Comparison of Tables 4 and 5 shows that there is a coupled decline of striatal ^{18}F -dopa and ^{11}C -NMF uptake in MSA and PD. Mean levels of putamen uptake of these two tracers are reduced to 40% of normal in both disorders. The simplest explanation for this finding is that it is a consequence of the loss of nigrostriatal nerve terminals known to occur in these akinetic-rigid syndromes. It has been shown that in PD at postmortem there is a 60–80% loss of pigmented cells from the substantia nigra (Rinne *et al.*, 1989). This parallel decline in dopamine storage and reuptake capacity may be relevant to the development of on-off responses to L-dopa therapy in severely affected PD subjects. If these patients are unable to reaccumulate dopamine after its release from the synaptic terminals in the striatum they will require plasma levels of L-dopa that are maintained in the therapeutic range in order to enable dopamine to be generated continuously in the striatum. It has been shown that intravenous infusions of L-dopa provide better clinical control than oral administration in on-off PD subjects (Nutt and Woodward, 1986).

The poorly L-dopa responsive MSA, and highly L-dopa responsive PD patients, showed an equally severe 60% reduction of mean putamen ^{18}F -dopa and ^{11}C -NMF uptake. Caudate ^{18}F -dopa and ^{11}C -NMF uptake was also significantly impaired in MSA, but there was relative sparing of caudate function in PD. Six out of 8 PD subjects had caudate ^{18}F -dopa uptake that was more than double that of the putamen. Caudate and putamen ^{18}F -dopa uptake was similarly affected in 5 out of the 10 MSA patients, while the other 5 subjects showed a similar pattern to the PD patients with relative sparing of caudate function. The 5 MSA patients with severely affected caudate function did not differ significantly from those with spared caudate function in either disease severity or duration.

While increased involvement of the caudate presynaptic dopaminergic system was present in the MSA patients compared with the PD patients, this does not explain the resistance of MSA patients to L-dopa therapy. Their poor L-dopa response is likely to reflect loss of postsynaptic rather than presynaptic connections. The integrity of postsynaptic dopaminergic receptors was not assessed in this present study.

The finding of a relative sparing of caudate function in PD is in agreement with histochemical data. Kish *et al.* (1988) noted relative preservation of caudate dopamine levels in autopsy specimens from PD subjects. It has been reported that the greatest nigral cell loss in PD is of the less pigmented cells in lateral substantia nigra compacta (German *et al.*, 1989; Gibb *et al.*, 1990). The cells in lateral substantia nigra compacta are known to project to the putamen, but why they should be particularly susceptible to Lewy body degeneration remains unclear. In MSA more global nigral degeneration occurs in the absence of Lewy body formation (Bannister and Oppenheimer, 1972). It is consequently not surprising that MSA patients show a greater disruption of their nigrocaudate dopaminergic system. We found, however, an overlap between the ranges of caudate Ki values that are obtained for ^{18}F -dopa uptake in the PD and MSA groups. A reasonable conclusion from our study is that if caudate and putamen ^{18}F -dopa uptake are equally severely affected, the patient is more likely to have MSA than PD.

Our findings suggest that impairment of the function of the presynaptic dopaminergic system in putamen, but not caudate, correlates with degree of locomotor disability. This finding fits in with current theories on the role of the basal ganglia in controlling motor actions (Alexander *et al.*, 1986). Electrophysiological and metabolic studies on primates have suggested that sequences of motor actions are programmed in the supplementary motor area (SMA) of the cortex. The sensorimotor cortex has a direct excitatory input into the putamen, which in turn sends efferents back to the SMA and other premotor areas via the pallidum and thalamus. By contrast, the caudate receives its input from frontal association areas, and sends efferents via the pallidum and thalamus to the prefrontal association cortex. It is consequently not surprising that putamen rather than caudate function directly correlated with locomotor status in our MSA subjects.

Severity of autonomic dysfunction has been shown to correlate with cell loss from the intermediolateral columns of the spinal cord in MSA and PAF (Oppenheimer, 1980). It is, therefore, not surprising that we found no correlation between disruption of the nigrostriatal dopaminergic system and clinical duration of autonomic dysfunction in the MSA patients. Mean striatal ^{18}F -dopa uptake in 7 patients with PAF was normal. This finding is against PAF and MSA, or PAF and PD, being overlap syndromes, despite the presence of cell loss from the intermediolateral columns of the spinal cord, and the presence of Lewy bodies in the pigmented brainstem nuclei and sympathetic ganglia in PAF. One of the 7 PAF subjects (Case 14) had levels of striatal ^{18}F -dopa uptake that were reduced to more than 2.5 SDs below the normal mean. This subject, aged 63 yrs, had symptoms of autonomic dysfunction for 7 yrs before the PET study, without evidence of extrapyramidal problems. Interestingly, 1 yr after PET, he has now developed severe nocturnal stridor typical of that seen in MSA, and it remains to be seen whether parkinsonism will develop in this patient. It has been estimated that clinical symptoms of parkinsonism only develop after loss of 80% of the normal putamen dopamine content (Marsden, 1982).

In summary, we have shown that function of the nigrostriatal dopaminergic system

is equally severely impaired in the putamen of MSA and PD subjects, but caudate function is significantly spared in PD. Patients are more likely to have MSA than PD if the caudate and putamen are equally severely affected. Locomotor disability correlates inversely with putamen, but not caudate, ^{18}F -dopa uptake. Striatal dopaminergic function is normal in the majority of PAF subjects, suggesting that PAF is not one extreme end of an overlap syndrome with PD or MSA, in spite of certain pathological similarities. PET is, however, capable of detecting subclinical striatal dysfunction when present in PAF patients.

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SPINAL CORD TRAUMA IN MAN: STUDIES OF PHOSPHORYLATED NEUROFILAMENT AND UBIQUITIN EXPRESSION

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SUMMARY

Changes in neuronal proteins are a major feature of the neurodegenerative disorders, but the biological significance of these changes is not understood. We describe alterations in neuronal proteins as a result of surgical tractotomy on the human spinal cord at 3, 5, 7, 14 and 72 days after operation. Antibodies to phosphorylated neurofilaments labelled neuronal cell bodies in the nucleus dorsalis and anterior horns. Axonal swellings showed positive staining for ubiquitin, but ubiquitinated neuronal inclusions were not evident. The presence of phosphorylated neurofilaments in the neuronal cell bodies and of ubiquitination of axonal swellings may be indicators of interrupted axonal transport. The changes found in intracellular proteins in neurons after trauma do not resemble those found in motor neuron disease, suggesting that the intraneuronal ubiquitinated inclusions may have a unique significance in the cytopathology of that disorder.

INTRODUCTION

Antibodies to cytoskeletal and other cellular proteins have been used to document a range of abnormalities in neurodegenerative disorders. Neuronal inclusions characteristic of Alzheimer's, Parkinson's and Pick's diseases have been shown to contain cytoskeletal components including neurofilaments (Anderton *et al.*, 1982; Gambetti *et al.*, 1983; Kahn *et al.*, 1985). Phosphorylated neurofilament epitopes are reported to accumulate in motor neuron disease (Manetto *et al.*, 1988b; Munoz *et al.*, 1988). Ubiquitin, a protein thought to play an important role in the nonlysosomal removal of aberrant and short-lived proteins from the cell, has received considerable attention following its localization in Alzheimer's tangles (Cole and Timiras, 1987; Mori *et al.*, 1987; Perry *et al.*, 1987) and subsequently in Lewy bodies of Parkinson's disease (Kuzuhara *et al.*, 1988). Previously unrecognized inclusions in the anterior horn cells of patients with motor neuron disease have been identified using antibodies to ubiquitin (Leigh *et al.*, 1988; Lowe *et al.*, 1988).

Although it has been suggested that these cytological abnormalities in neurodegenerative disorders may have specificity in relation to the pathogenesis of these disorders, their biological significance is uncertain (Leigh *et al.*, 1988, 1989). The pathogenesis of the changes in the anterior horn cells in motor neuron disease might be better understood if the biological specificity of the abnormalities found in neurofilament proteins and other cytoskeletal and cytoplasmic proteins was better characterized. We therefore

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undertook a study of the response of the human spinal cord to therapeutic spinothalamic tractotomy as a disease control for the study of neurodegenerative disorders. This model of central nervous system trauma is particularly useful since both the mechanism of injury and its time course are known.

MATERIAL AND METHODS

Five cases of spinal cord trauma resulting from open surgical (4 cases) or percutaneous (1 case) cordotomy for the relief of intractable pain were identified from the records of the Department of Morbid Anatomy during the years 1964–1974. Five age-matched normal controls were also studied. The time from injury to time of death, mode of death and postmortem delay was noted for all cases. All available spinal cord blocks in cases of trauma were used in order to study changes at above and below the level of injury (*see Table*).

Sections were cut from formalin-fixed paraffin embedded material. A standard indirect immunoperoxidase method was used to study the pattern of staining with the following antibodies. (1) MAB 147, a monoclonal antibody with specificity for the highly phosphorylated 210 kD neurofilament protein which is found in axons but not neuronal cell bodies in normal tissue (Anderton *et al.*, 1982, Haugh *et al.*, 1986). (2) Anti-glial fibrillary acidic protein (GFAP), a commercially available monoclonal antibody raised against the bovine glial protein (DAKO-UK). This antibody demonstrates astrocytes, but not neurons or microglia. (3) Anti-ubiquitin, an affinity purified polyclonal antibody (Leigh *et al.*, 1988) which demonstrates accumulations of ubiquitin such as those found in association with neurofibrillary tangles in Alzheimer's disease, intraneuronal inclusions in motor neuron disease and other cellular inclusions (Leigh *et al.*, 1988; Lowe *et al.*, 1988; Manetto *et al.*, 1988a).

TABLE CLINICAL DATA

<i>Sex, age (yrs)</i>	<i>Survival (days)</i>	<i>Primary diagnosis</i>	<i>Cause of death</i>	<i>Level of cordotomy</i>	<i>Blocks available</i>
M, 54	3	Carcinoma of lung	Respiratory insufficiency	T1	C8, T1, T2
M, 46	5	Salivary gland tumour	Pneumonia	C2	C1, C2, C3, C6, C7
M, 56	7	Carcinoma of rectum	Cardiac arrest	T5, T6 (bilateral)	T4, T5, T6, T7
M, 65	14	Carcinoma of lung	Respiratory insufficiency	C2 (bilateral)	C1, C2, C3, L2
M, 64	72	Carcinoma of lung	Respiratory insufficiency	C2	C1, C2, C3, T4, T5

The sections were incubated overnight at 4° C with primary antibody and then peroxidase-antiperoxidase complex was applied. Staining was developed with diaminobenzidine in hydrogen peroxide. In each case control sections were included in which the primary antibody was omitted and sections with a known pattern of positive staining were also included; for example, sections from cases of motor neuron disease with ubiquitinated neuronal inclusions. Sections were also processed for silver impregnation (using the Gleebs-Marshall technique), Luxol-fast blue, and haematoxylin and eosin (H and E) staining.

The sections were studied by 2 pathologists unaware of the clinical history. Observations were made on the light microscopical appearance at the level of the lesion and cephalad and caudal to this point (*Table*).

RESULTS

Histology

In all 5 cords examined after cervical cordotomy the lesion involved the lateral funiculus including the posterior spinocerebellar, lateral corticospinal and lateral spinothalamic

tracts. Two showed changes which, although unilateral, often affected larger cross-sectional areas of the cord, including the anterior segments and posterior columns. In 2 other cases there were bilateral lesions (Table).

In cords studied at 3, 5 and 7 days after tractotomy lateral pial disruption was present at the level of the lesion and foci of necrosis and haemorrhage were seen in the white matter in which disintegration of axons and myelin was evident. In these cords and in the cord examined 14 days after surgery there was distortion of the white matter in the area of the lesion by oedema of the neuropil (seen as an expansion of the perivascular and perineuronal spaces) and axonal swellings in addition to those normally present in the cord (fig. 1). These changes extended for several segments above and below the level of the lesion. The axonal swellings were large (up to 50 μm in diameter) and similar

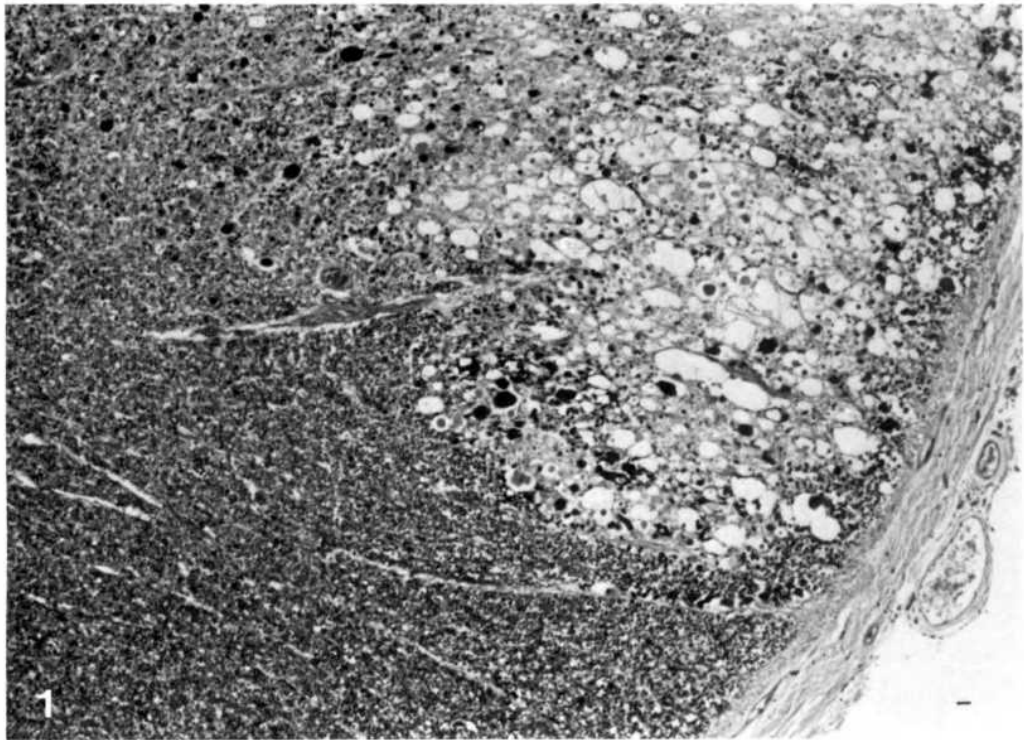


FIG. 1. Lateral part of cervical spinal cord 5 days after cordotomy. Axonal swellings and oedema are prominent, MAB 147 immunoperoxidase. Bar = 10 μm .

in appearance to the axonal retraction balls seen after head injury, and after cryogenic spinal cord injury in the rat (Collins *et al.*, 1986). Axonal swellings were seen in silver impregnations, and the Luxol-fast blue stain demonstrated myelin pallor in the affected areas. In these areas the myelin showed a range of degenerative changes from vesiculation to fragmentation. In the cord examined 72 days after surgery occasional mildly swollen axons were seen, but no large axonal swellings were present.

In the grey matter, areas of necrosis were present in those cases showing more extensive lesions. The lateral parts of the anterior and posterior horns were mainly affected. Neuronal cell bodies at the edges of necrotic areas showed chromatolysis with swollen cell cytoplasm and eccentric nuclei. The remaining neurons appeared normal. No intraneuronal inclusions or neurofibrillary changes were noted in any case of trauma or in any control.

Glial reaction varied with the degree and timing of the injury. In the more severely necrotic areas in the acute phase of injury (3, 5 and 7 days after surgery), astrocytes and oligodendrocytes were not seen. At the margins of the lesion in the cords 3, 5, 7 and 14 days after tractotomy, however, there was an astrocytic reaction and in the cord examined 72 days after tractotomy gliosis was seen at the margin of the lesion. Corpora amylacea were seen in the neuropil, chiefly in the white matter, both in cases and in controls.

Immunostaining

Positive staining for GFAP was seen in the area of gliosis at the site of cordotomy after 72 days but not in other cases. Axonal swellings were not stained. GFAP positive staining was otherwise seen in the usual distribution of astrocytes.

In the cordotomy cases, dense staining for phosphorylated neurofilaments using MAB147 was seen in the majority of axonal swellings (fig. 1) and this was also seen in the cord examined 72 days after injury with the few remaining small swellings still staining positively. At 3, 5, 7 and 14 days after injury, both at the level of damage and in adjacent segments, neuronal cell bodies in the anterior horn and Clarke's column reacted positively for phosphorylated neurofilament epitopes. The staining in these neuronal cell bodies was evenly distributed with no clumping or focal positivity. Positive staining was also seen, as expected, in normal axons in all sections studied (figs 2, 3). Phosphorylated neurofilaments were not seen in the neuronal cell bodies of controls.

Using antiubiquitin antibody there was a diffuse pattern of positivity in large axonal swellings in the cords examined at 3, 5, 7 and 14 days after tractotomy (fig. 4), and pale, diffuse staining in the smaller 'normal' swellings seen in cases and controls. Diffuse staining of corpora amylacea was seen in both cases and controls. No ubiquitin positive neuronal inclusions were seen in any case.

DISCUSSION

The changes that develop in damaged neurons and axons in the traumatized spinal cord provide a model for neuronal protein changes secondary to disease or 'stress-induced' changes, since the nature of the insult and the timing of the injury are clear. Previous studies of the development of the morphological features after injury to the spinal cord have utilized animal models (Collins *et al.*, 1986; Balentine, 1988).

Our series comprised patients in whom open surgical or percutaneous tractotomy had been performed. The spinal cords were examined 3, 5, 7, 14 and 72 days after surgery. The morphological responses following injury to the spinal cord in our cases are similar to those previously described in both animals and humans, and consist of oedema, axonal swelling or ballooning, microglial and astrocytic reaction and subsequent gliosis (Collins *et al.*, 1986; Hughes, 1978).

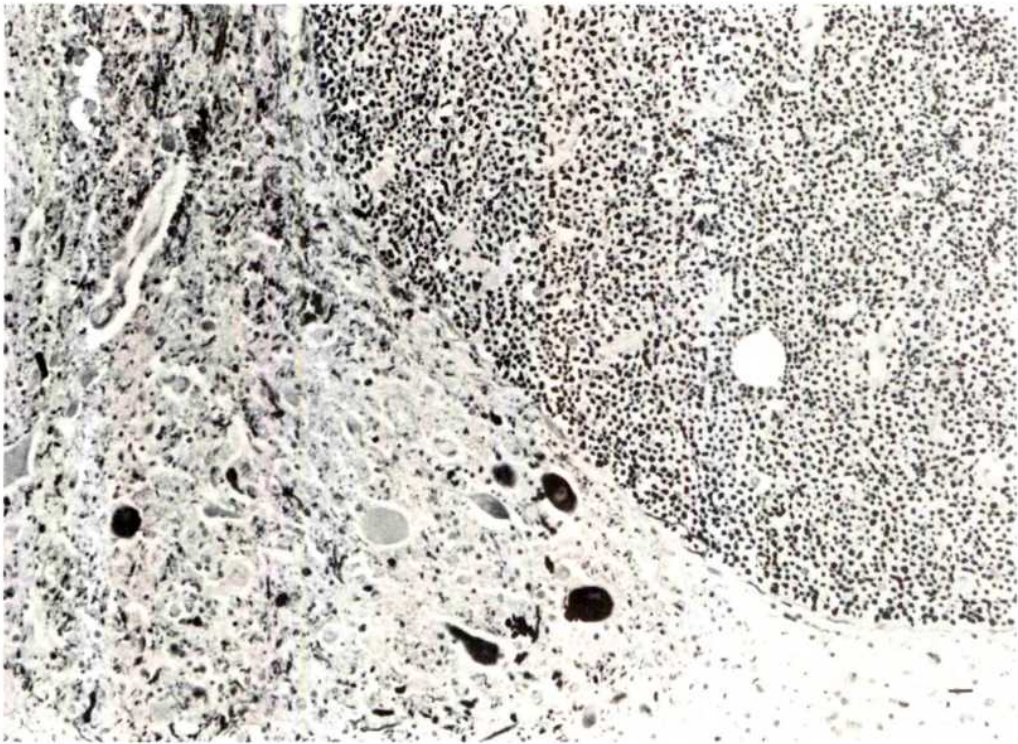


FIG. 2. Phosphorylated neurofilament epitopes labelled in neuronal cell bodies in Clarke's column. MAB 147 immunoperoxidase. Bar = 10 μ m.

In our cases of spinal cord trauma phosphorylated neurofilaments were found in axonal swellings and also in neuronal cell bodies in the nucleus dorsalis and anterior horn both at the level of the lesion and in adjacent segments. These changes were seen from 3 to 14 days after injury, but were not present 72 days after surgery. Neurofilaments (NF) are part of the neuronal cytoskeleton and are composed of low (68 kD), medium (145 kD) and high (200 kD) molecular weight proteins, with the high molecular weight NF generally showing a high degree of phosphorylation (Carden *et al.*, 1985). Nonphosphorylated neurofilament proteins are normally seen in the perikaryon and dendrites of neurons, whereas those in axons are phosphorylated (Sternberger and Sternberger, 1983; Lee *et al.*, 1987).

Phosphorylation of neurofilaments in neuronal perikarya occurs in the rat dorsal root ganglia after crush, but not after transection injury to the sciatic nerve (Rosenfeld *et al.*, 1987). In our cases the lesion consisted of surgical spinal tractotomy producing axonal transection; in these cases the neuronal perikarya labelled with antibody to phosphorylated neurofilament epitopes, a finding at variance with the experimental work on transected rat sciatic nerve (Rosenfeld *et al.*, 1987). The distribution of the phosphorylated cell bodies was consistent with a secondary response to axonal damage, even when the neuronal cell bodies were not themselves involved, as in neuronal

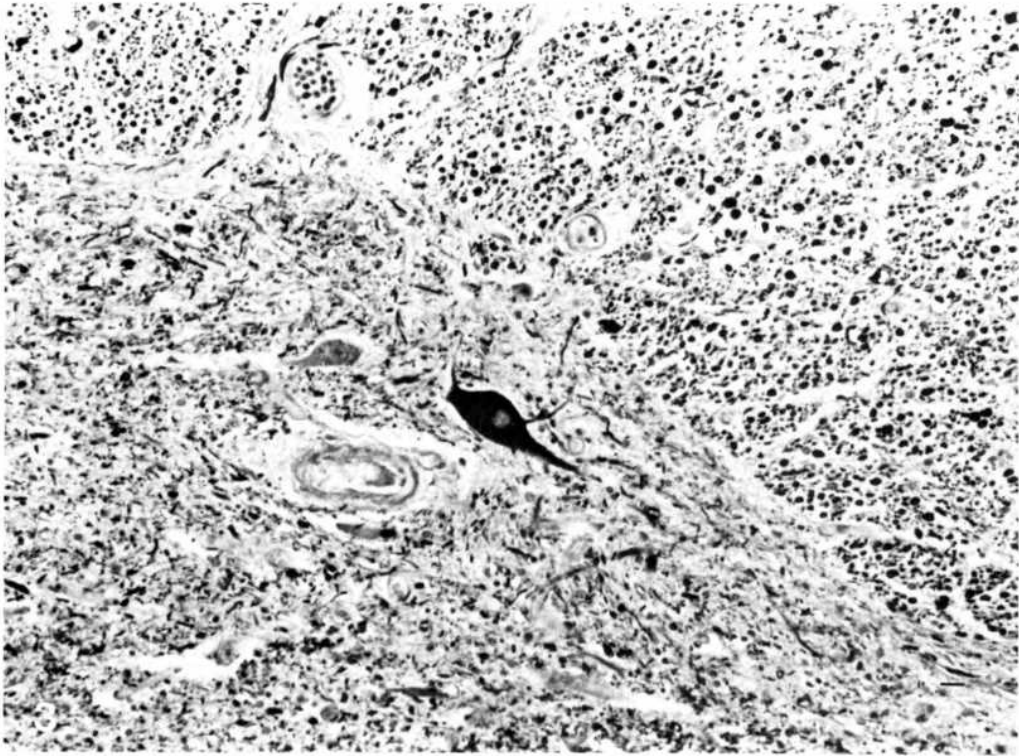


FIG. 3. Phosphorylated neurofilament epitopes labelled in an anterior horn cell. MAB 147 immunoperoxidase. Bar = 10 μ m.

chromatolysis following axotomy (Goldstein *et al.*, 1987). The neuronal changes in the nucleus dorsalis may thus be a direct result of transection of axons in the posterior spinocerebellar tract. Transection of the lateral corticospinal tracts, however, would not involve direct severance of anterior horn cell axons although it is possible that anterior roots may have been injured or irritated during surgery. There is no evidence that damage to the upper motor neuron can lead to disruption of axonal transport in the lower motor neuron.

Phosphorylated neurofilaments in neuronal cell bodies have been found in a variety of conditions, including Alzheimer's disease (Sternberger and Sternberger, 1983; Cork *et al.*, 1986), Parkinson's disease (Forno *et al.*, 1986), aluminium intoxication (Bizzi and Gambetti, 1986; Troncoso *et al.*, 1986), and experimental intoxication with β,β' -iminodipropionitrile (Cork *et al.*, 1986). Alteration of the usual pattern of phosphorylated neurofilaments has also been reported in motor neuron disease (Manetto *et al.*, 1988b), although these findings were not confirmed in the study of Leigh *et al.* (1989). These changes have generally been associated with premature NF phosphorylation, either resulting from an alteration in NF transport from the perikaryon into the proximal axon (Manetto *et al.*, 1988b) or, as a primary defect, leading to such an abnormality in NF transport. In hereditary canine spinal muscular atrophy there is

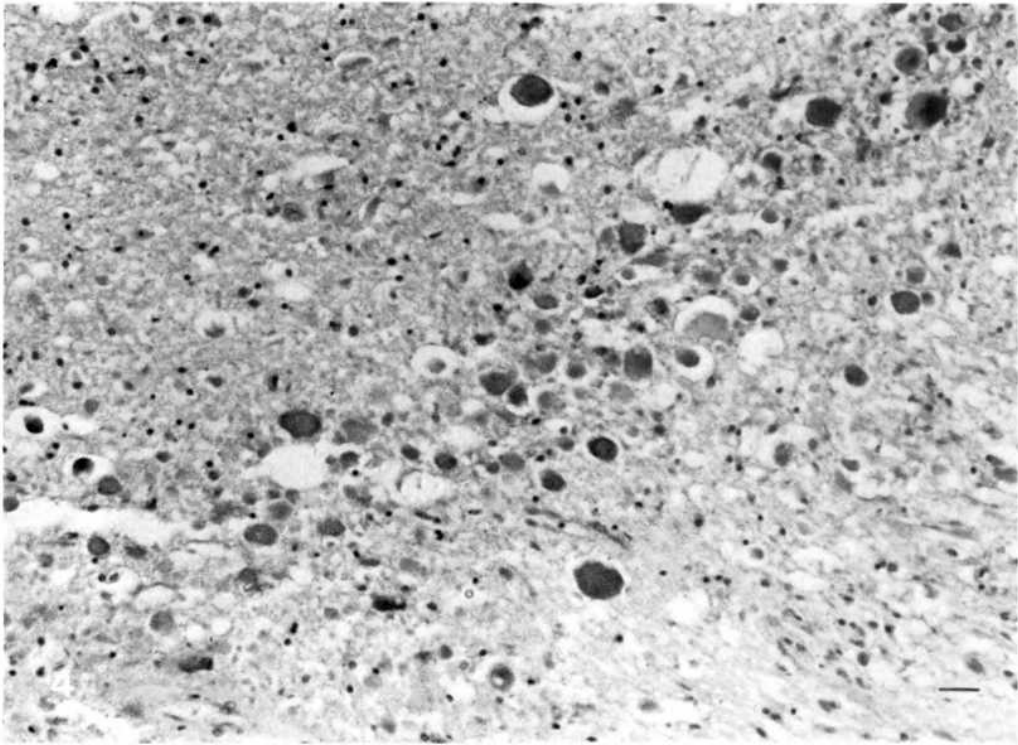


FIG. 4. Diffuse labelling of large axonal swellings using antiubiquitin antibody, 14 days after cordotomy. Immunoperoxidase. Bar = 10 μ m.

disordered axonal transport (Griffin *et al.*, 1982) and phosphorylated neurofilaments are found in lower motoneuron perikarya (Cork *et al.*, 1988). Our findings in spinal cord tractotomy in man support the concept that the abnormality in distribution of phosphorylated neurofilaments is secondary to an alteration in NF transport, in our cases caused by axonal transection or disturbance.

We observed diffuse labelling of large axonal swellings by antiubiquitin antibody after spinal tractotomy, but ubiquitinated neuronal inclusions resembling those found in motor neuron disease (Leigh *et al.*, 1988) were not found. Ubiquitin is a small polypeptide which plays a role in targeting proteins for degradation via a nonlysosomal proteolytic system (Finley and Varshavsky, 1985). Ubiquitin is covalently bound to target proteins, and has been demonstrated immunohistochemically in association with a variety of intracellular inclusions, such as Lewy bodies in Parkinson's disease (Kuzuhara *et al.*, 1988) and the neurofibrillary tangles of Alzheimer's disease (Cole and Timiras, 1987; Mori *et al.*, 1987; Perry *et al.*, 1987). Ubiquitin has been shown to stain discrete rounded and skein-like inclusions with anterior horn cells in motor neuron disease (fig. 5), and diffuse staining is seen in the axonal swellings found in this disorder (Leigh *et al.*, 1988; Lowe *et al.*, 1988). The axonal swellings associated with cordotomy contain phosphorylated neurofilaments, as do the axonal swellings in motor neuron disease,

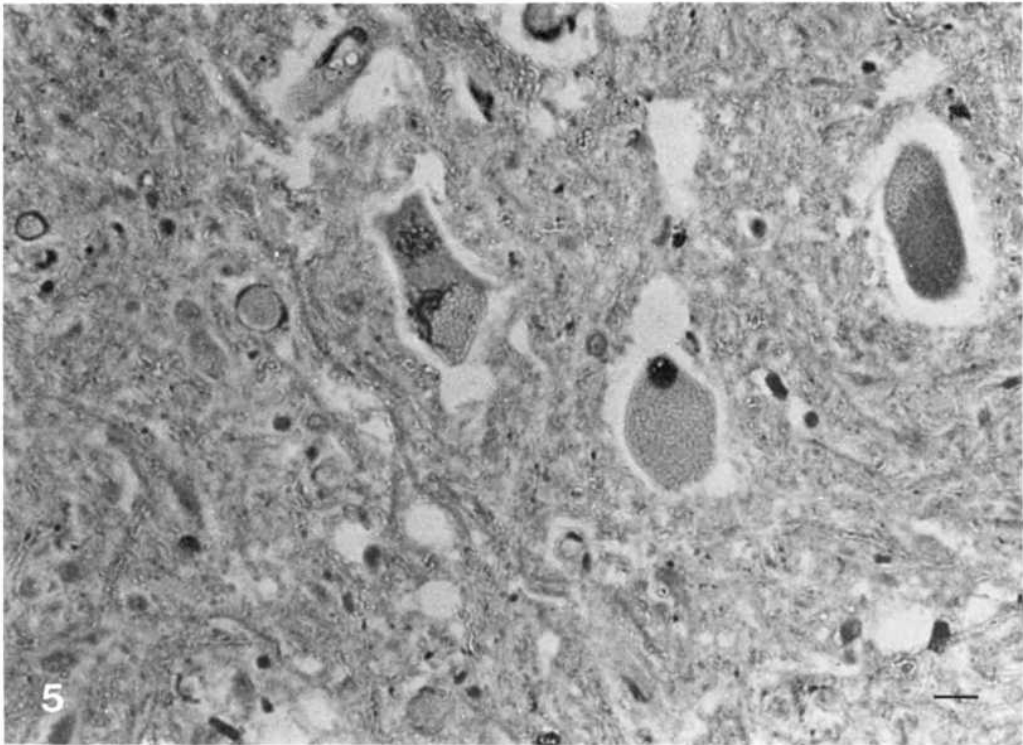


FIG. 5. Rounded and skein-like intraneuronal inclusions in a case of motor neuron disease, demonstrated using antiubiquitin antibody (Leigh *et al.*, 1988; Lowe *et al.*, 1988). Immunoperoxidase. Bar = 10 μ m.

and show a similar pattern of staining for ubiquitin. However, the neurons in the anterior horns in the cases of spinal cord trauma did not contain ubiquitinated inclusions. The absence of axonal swellings and ubiquitin staining in the cord examined 72 days after tractotomy suggests that the axonal lesion seen in earlier cases represents an initial response to trauma, and that as the lesion resolves or is degraded, the ubiquitinated material is removed. The absence of inclusions in neuronal cell bodies in the cords examined after cordotomy, despite the presence of phosphorylated neurofilaments in the perikarya and of ubiquitin in axonal swellings, suggests that the ubiquitinated neuronal inclusions seen in motor neuron disease reflect primary neuronal abnormalities, rather than an effect secondary to disruption of axonal transport. The presence of phosphorylated neurofilaments in neuronal perikarya and ubiquitin in axonal swellings may be common to any process that causes interruption of axonal transport.

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VOLUNTARY ACTIVATION OF HUMAN MOTOR AXONS IN THE ABSENCE OF MUSCLE AFFERENT FEEDBACK

THE CONTROL OF THE DEAFFERENTED HAND

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SUMMARY

The ability to activate human motoneurons supplying individual intrinsic muscles of the hand was examined during acute deafferentation of the muscles. Tungsten microelectrodes were inserted percutaneously into motor fascicles of the ulnar nerve of 5 subjects, which was then blocked distally with local anaesthetic. In 4 subjects unitary action potentials were recorded from 16 motor axons, which were identified with respect to their target muscles. In the complete absence of muscle afferent feedback, subjects could voluntarily recruit motoneurons, grade their discharge and sustain a constant level of activity. Significant facilitation of motor efforts was provided by cutaneous feedback from the digits via the median nerve. During attempted maximal voluntary efforts the mean discharge frequencies of single motor axons were significantly lower than those of normally-innervated motor units. This finding suggests that peripheral afferents have a net facilitatory influence on motoneurons. However, during prolonged (20–30 s) maximal voluntary efforts the deafferented motoneurons did not display the progressive decline in discharge frequency shown by normally-innervated motor units during contractile fatigue, a finding consistent with two possible explanations: disfacilitation or reflex inhibition of the motoneuron pool by peripheral afferents. The results also indicate that the otherwise intact nervous system can perform some simple motor tasks with no proprioceptive input other than knowledge of the motor commands. Other factors may contribute to the poor motor performance reported for patients with severe sensory deficits.

INTRODUCTION

Given that low-threshold muscle afferents provide conscious signals of limb position and movement (e.g., Goodwin *et al.*, 1972; Roll and Vedel, 1982; Gandevia, 1985), and possibly also of intramuscular tension (McCloskey *et al.*, 1974; Rymer and D'Almeida, 1980), it might be expected that intramuscular receptors are critical for the ability to control the output of a motoneuron pool. Surgical deafferentation in subhuman primates results in severe deficits in motor control, particularly in the execution of distal movements (e.g., Mott and Sherrington, 1895; Munk, 1909; Lassek, 1953; cf Knapp *et al.*, 1963; Bossom, 1974; Polit and Bizzi, 1979). Clinical studies of patients

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following sensory loss have also noted specific deficits in motor performance, although maximal strength does not appear to be affected markedly (Bastian, 1887; Rothwell *et al.*, 1982; Jeannerod *et al.*, 1984; Sacks, 1985; Cole *et al.*, 1986; Forget and Lamarre, 1987; for review, *see* Sanes *et al.*, 1985). Patients with chronic sensory neuropathies affecting large myelinated afferents cannot maintain force or position accurately when visual cues of their performance are removed (Rothwell *et al.*, 1982; Sanes *et al.*, 1985; *cf* Cole *et al.*, 1986). Whether the poor motor performance results from a loss of input from muscle, joint or cutaneous afferents is not known. However, because motor deficits were not evident when the digital nerves were anaesthetized in normal subjects, Rothwell *et al.* (1982) concluded that the input from muscle spindles and Golgi tendon organs is necessary for the normal control of motor output.

In contrast to the deficiencies documented during deafferentation, those motor capacities that are preserved provide some clues about the awareness of volitionally generated motor commands. Such signals contribute to sensations of force and heaviness (e.g., McCloskey *et al.*, 1974; Gandevia and McCloskey, 1977*a-c*; *see also* McCloskey, 1981; Gandevia, 1987). In a recent study Gandevia and Rothwell (1987) demonstrated that normal subjects could learn to direct 'liminal' motor commands to intrinsic muscles of the hand, insufficient to recruit motoneurons in the target pool, and therefore without reliance on a change in the afferent input from the limb.

The present study employed microneurographic techniques to examine the discharge behaviour of motoneurons supplying intrinsic muscles of the hand. The activities of individual motor axons in the ulnar nerve were recorded proximal to a complete anaesthetic block of the nerve, that is, in the complete absence of feedback from the target muscle. This novel approach allowed us to address the relative importance of afferent information from intramuscular receptors in the execution and control of movements of the hand. In addition, the experimental design allowed us to examine the facilitatory (Hagbarth *et al.*, 1986) and inhibitory (Bigland-Ritchie *et al.*, 1983) reflex effects ascribed to muscle afferents. Some preliminary observations have been presented (Burke *et al.*, 1988*a*; Gandevia *et al.*, 1989).

METHODS

The major microneurographic data were obtained from 11 of 14 experimental sessions on the ulnar nerves of 5 subjects, including the authors (aged 26–44 yrs). The procedures used were specifically approved by the institutional ethics committee. Additional electromyographic (EMG) studies performed in 4 of the subjects are detailed below.

Microneurographic studies

The subject was seated comfortably with forearm and hand resting supine on a padded table. The ulnar nerve was located about 10–12 cm proximal to the wrist by electrical stimulation. An insulated tungsten microelectrode was inserted percutaneously into the nerve and its position adjusted while delivering stimuli (0.1 ms pulses, 0–15 V, 1 Hz) through the microelectrode until a motor fascicle, supplying one or more of the intrinsic muscles of the hand, was entered. Intrafascicular stimulation at these sites evoked strong muscle contraction but no radiating cutaneous paraesthesiae, and occasionally deep and unpleasant sensations in one or more metacarpophalangeal joints (*see* Burke *et al.*, 1988*b*). When recording at these sites, crisp afferent responses were evoked by percussion and stretching of the relevant muscle (e.g., Burke *et al.*, 1988*b*) but no activity was evoked by cutaneous stimulation within the distribution of the dorsal or digital branches of the ulnar nerve.

Once a suitable site had been secured, the evoked afferent responses were monitored while the ulnar nerve *distal* to the recording site was blocked with 5–10 ml of 2% lignocaine (with adrenaline) injected around the nerve about 2 cm proximal to the wrist. The block of the ulnar nerve was clinically complete within 15–30 min: tactile, pain and temperature sensations were lost in the digital and dorsal innervation zones, and the intrinsic muscles of the hand that receive ulnar innervation were paralysed. In addition, the muscle afferent responses to percussion and stretch were abolished as the block developed, as were the motor responses in the intrinsic muscles produced by intrafascicular stimulation (fig. 1). To confirm the completeness of the block, stimulus intensities of up to 12 V were used, up to three times greater than those initially required to produce a maximal twitch response to intrafascicular stimulation before the anaesthetic block. These stimuli often produced deep pain referred to specific metacarpophalangeal joints, much as was evoked by intense stimuli before the block. This provided indirect evidence that the microelectrode position had remained stable.

When the block was complete the subject attempted to make simple movements which would have activated the muscles under study. After studying the motor behaviour of multiunit activity, fine manipulations of the microelectrode were then made during attempted movements to focus the recording on the activity of a single axon. Clearly, voluntarily activated axons recorded proximal to the block must be motor axons. The majority of the recordings from motor axons were obtained after only minimal adjustments in the position of the microelectrode from its initial intrafascicular site. Once isolated, the behaviour of each unit was examined in a detailed sequence of attempted voluntary manoeuvres, including attempted flexion and extension of metacarpophalangeal and interphalangeal joints and abduction and adduction of the relevant digits. This was done to check the actions which recruited the unit and thus to establish the destination of the motor axon.

Recording and data analysis

Neural activity was amplified (2×10^4), filtered (0.3–8.0 kHz) and recorded on magnetic tape for subsequent analysis, together with surface EMG (8–800 Hz) from relevant muscles of the paralysed hand. In some studies subjects were requested to match the efforts directed to the paralysed muscle by an identical contraction of the homologous contralateral muscle (see fig. 2), and the forces so generated were measured by a strain gauge and recorded on tape. Multiunit activity was integrated (time-constant 200–500 ms) and displayed on an electrostatic recorder. During reanalysis of the neural data the signals were high-pass filtered (0.5–0.7 kHz) and potentials discriminated using a dual amplitude/time window (Bak Electronics). All accepted unitary action potentials were displayed on storage oscilloscope and photographed. Acceptance pulses from the signal discriminator were displayed on an ink-jet recorder via an instantaneous frequency meter and recorded on a laboratory microprocessor for the generation of interspike interval data (resolution 1 ms) and the production of time-interval histograms (4 ms bins). Interspike intervals shorter than 8 ms (i.e., 'doublets') and longer than 200 ms (i.e., less than 5 Hz) were excluded. Further analysis of the neural data was performed on a digital acquisition and analysis system (MS20, Medelec). This programmable system allowed sampling of the neural signals at 20 kHz (sweep duration 5 ms), delayed display of the unitary action potentials, and analysis of spike train data (see fig. 3).

Paired *t* tests or the Mann-Whitney *U* test were employed for statistical evaluation of the data. Differences were considered significant at $P < 0.05$.

Electromyographic studies

In a separate series of experiments in the same subjects, the discharge behaviour of motor units in the normally-innervated intrinsic muscles of the hand was examined during maximal voluntary contractions. Tungsten microelectrodes insulated with teflon were advanced manually into the first dorsal interosseous muscle during sustained (20–30 s), quasi-isometric, maximal voluntary contractions. Subjects were provided with loud verbal encouragement and auditory feedback of their EMG activity. Brief trains of single motor unit or muscle fibre action potentials were recorded (Freund *et al.*, 1975; Bigland-Ritchie *et al.*, 1983, 1986b; Hagbarth *et al.*, 1986; Woods *et al.*, 1987), stored on magnetic tape with the strain-gauge voltage, and analysed in an identical manner to the motor axon data.

RESULTS

Motoneuron behaviour during acute deafferentation of the target muscle

Efferent activity was recorded from motor fascicles of the ulnar nerve, proximal to a complete conduction block of the nerve at the wrist, in 11 experimental sessions in

5 subjects. The block was considered complete when there was anaesthesia and paralysis in the usual ulnar distribution. In addition, the afferent response to repeated muscle stretch was lost and intrafascicular stimulation at 2–3 times the control level failed to evoke activity in intrinsic hand muscles (*see* Methods and fig. 1). There was no evidence that the injection of local anaesthetic around the ulnar nerve involved the median nerve: cutaneous sensation in the median territory remained normal.

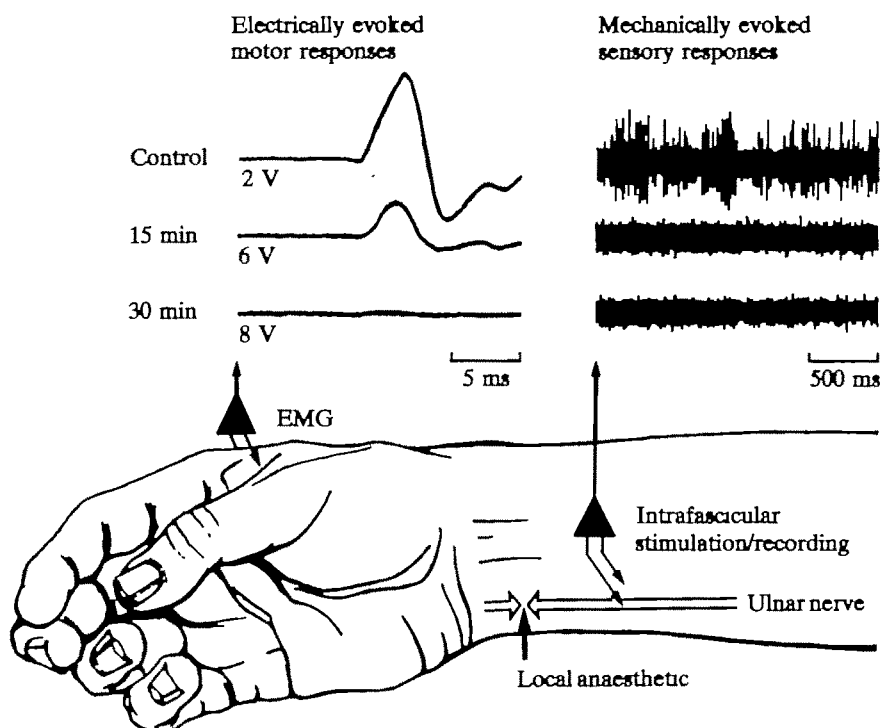


FIG. 1. Experimental methods for recording motoneuron activity in the absence of muscle afferent feedback. A tungsten microelectrode was inserted percutaneously into a motor fascicle of the ulnar nerve (here supplying first dorsal interosseus). The motor fascicle was defined by the motor response to intrafascicular stimulation through the microelectrode (*top left panel*) and by the activity recorded from low threshold muscle afferents evoked by stretch or percussion of the muscle (*top right panel*). At 15 min after injection of lignocaine around the nerve distal to the recording site the compound muscle action potential recorded from first dorsal interosseus was approximately one-third of its control value (supramaximal at 6 V, compared with 2 V before induction of the block) and the evoked afferent responses were abolished (*middle traces*). The block was complete at 30 min (*lower traces*).

Fig. 2 illustrates a multiunit recording from a fascicle innervating the adductor of the little finger, and the matching force simultaneously exerted by the contralateral muscle. When the subject was requested to attempt a sustained contraction of the muscle on both sides, the effort directed to the paralysed muscle, as reflected in the integrated neural activity, closely paralleled the actual force generated by the contralateral muscle. This provides further support to the conclusion of Gandevia and Rothwell (1987) that subjects

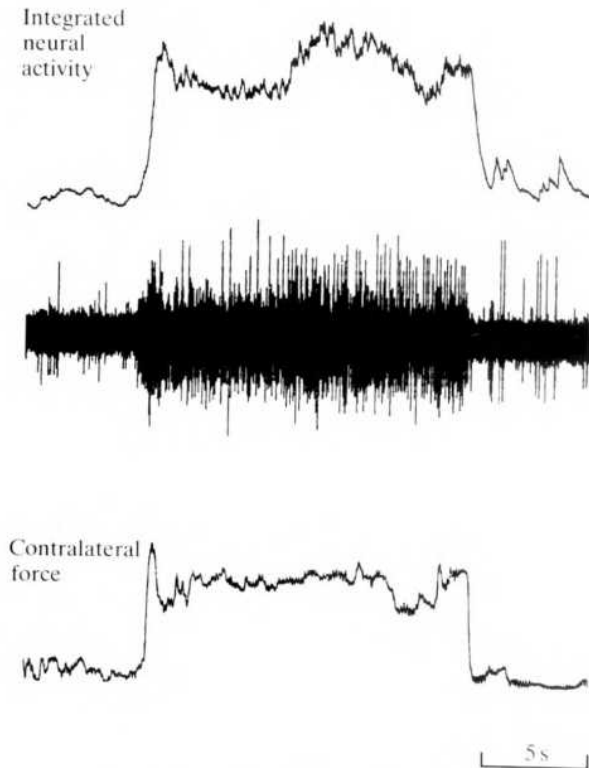


FIG. 2. Multiunit activity recorded from a fascicle supplying the fourth palmar interosseous during an attempted sustained strong contraction of the paralysed and deafferented muscle. The subject was instructed to direct his effort also to the contralateral, normally innervated, muscle. Note the bilateral fluctuations in 'effort', indicated by the largely parallel changes in integrated neural activity and contralateral force.

can focus their motor commands to a specific muscle in the absence of any change in peripheral feedback. Because simultaneous recordings from two motor fascicles were not made we cannot state that the voluntary effort was focused on a *single* intrinsic muscle. Subjects attempted simple acts such as flexion, abduction and opposition, but the last manoeuvre certainly involves more than one intrinsic muscle.

In 4 subjects unitary recordings were made from 19 motor axons. When subjects were completely relaxed no motor activity was recorded in the ulnar nerve, but many of the single motoneurons were of such low threshold that subjects often found it difficult to silence them. Sixteen of the motor axons were identified with respect to their target muscles in the hand, and each could be recruited during attempts to contract the relevant paralysed muscle (*see below*). The discharge behaviour of the remaining 3 motor axons, although similar to the others, was not fully characterized and will not be considered further. A representative record of the typical spike morphology of a single motor axon is illustrated in fig. 3A, which presents a raster of 50 consecutive action potentials obtained during a weak attempt to contract the paralysed adductor of the little finger. A highly stable recording from a motor axon in another subject is shown in fig. 3B. This axon was directed to adductor pollicis.

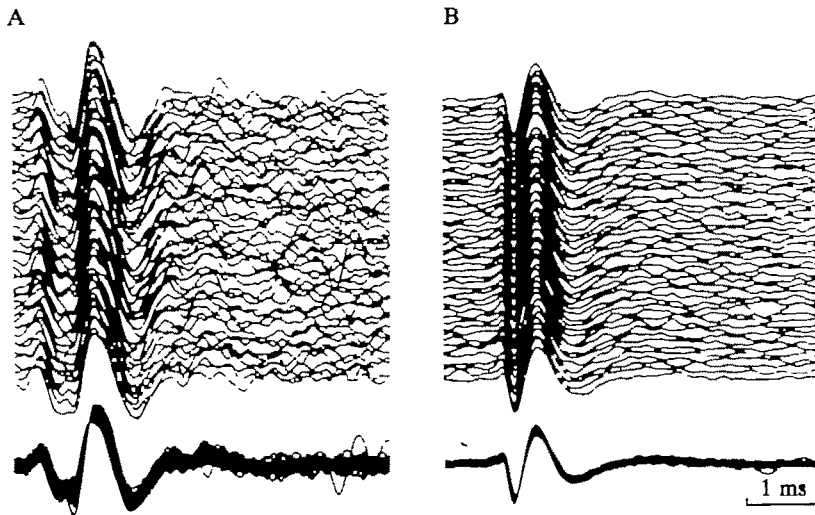


FIG. 3. Action potentials recorded from 2 motor axons during weak voluntary attempts to contract the appropriate paralysed muscle, with 50 sweeps (5 ms duration) shown as a raster (*upper traces*) and superimposed (*lower trace*), A, for adduction of digit V, B for adduction of digit I. The records in B are particularly stable, suggesting a very close extra axonal location of the electrode tip. The mean discharge frequencies were 5.3 Hz in A and 22.1 Hz in B, the coefficients of variation were 1.62 and 0.64, respectively.

An example of the procedures employed to determine the target muscle of each motor axon is provided in fig. 4. Prior to the nerve block, the afferent activity evoked by mechanical stimulation and the motor responses to intraneural microstimulation both revealed that the microelectrode was situated within a motor fascicle supplying an adductor, either of the ring finger or little finger. After the nerve block, the subject attempted to move each immobile digit in ways that would usually activate a specific muscle. In fig. 4, a motor axon that was activated during attempted quasi ballistic adductions of the relevant digit and during attempted flexions at its metacarpophalangeal joint, but not during attempted abduction or extension, was considered to innervate a palmar interosseous muscle (*see Gardner et al.*, 1975, for a description of the anatomical actions of the muscle). Because long flexor and extensor muscles within the forearm contract with flexion and

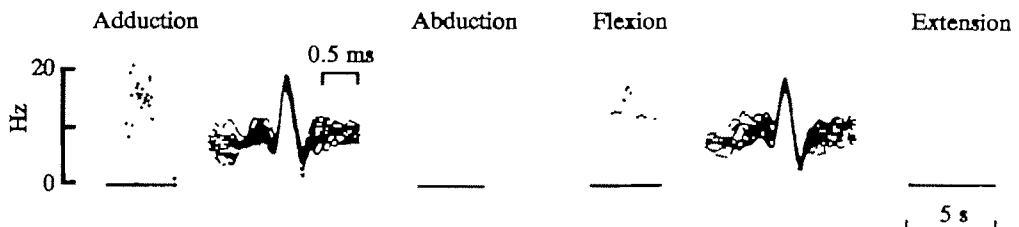


FIG. 4. Sequence of some of the attempted movements of the ring finger used to identify the target muscle of the motor axon. Instantaneous frequency records and superimposed action potentials illustrate the voluntary activation of the motoneuron during attempted adduction but not abduction of digit IV, and during attempted flexion but not extension at the metacarpophalangeal joint, consistent with the actions of third palmar interosseous muscle.

extension of the digits, emphasis was placed on recording from axons which innervated the palmar and dorsal interossei. Some effort was made to obtain recordings from motor fascicles innervating muscles on the radial aspect of the hand (e.g., adductor pollicis and first dorsal interosseous), so that cutaneous afferent feedback was intact (via the median nerve) while the ulnar block interrupted muscle afferent feedback.

Two of the 16 identified motor axons supplied adductor pollicis; 2 supplied the adductor of digit II (first dorsal interosseous) and 1 its adductor (second palmar interosseous); 4 supplied the lumbrical of digit III; 4 the adductor of digit IV (third palmar interosseous); and 2 units supplied the fourth palmar interosseous and 1 the lumbrical of digit V. Thus only the latter 3 axons (19% of the identified axons) were destined for muscles acting on the little finger, in which both cutaneous and muscle afferent information was completely interrupted (e.g., fig. 3A). Their behaviour was not notably different from that of the other motor axons. The 4 axons innervating the adductor of the ring finger were not deprived of appropriate cutaneous feedback because only the ulnar aspect of the ring finger was anaesthetized, that is, the side opposite to that on which the muscle acts.

Importance of auxiliary feedback

Subjects had access to the standard audiovisual monitoring of their neural discharge, and this kind of 'auxiliary feedback' was often important for the subject to know whether the central command was successful in activating a single motoneuron. The importance of providing auditory or visual feedback was examined by the unexpected removal of feedback either before or during an attempt to activate a motoneuron. For example, the motoneuron in fig. 3A could not be recruited in the absence of auditory or visual feedback. The motoneuron in fig. 5 rarely generated action potentials during maximal attempts to activate the motoneuron following the withdrawal of auxiliary feedback, whereas it fired at high discharge frequencies during weak efforts when feedback was provided. Presumably the subject was able to learn to focus voluntary effort on the relevant motoneuron pool

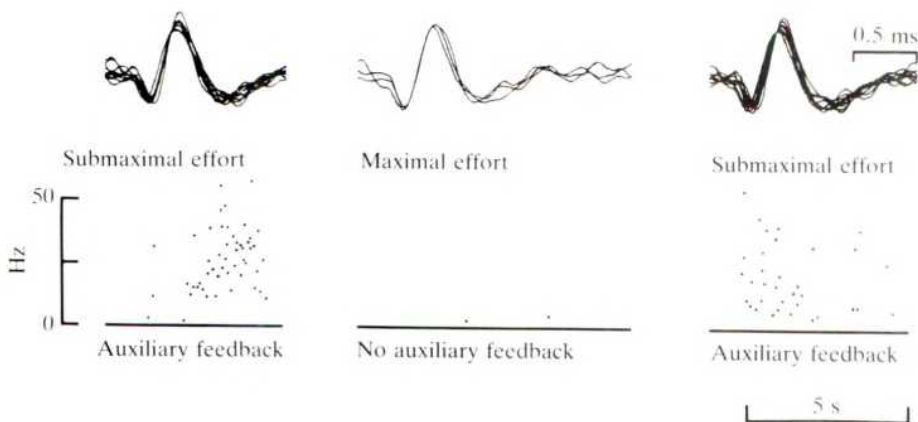


FIG. 5. Discharge behaviour of a motor axon during an effort (adduction of digit II) in which the subject was deprived of auditory and visual feedback of the motoneuron activity. In the presence of such auxiliary feedback the subject could recruit the motoneuron and generate high instantaneous frequencies at low levels of effort. In the absence of auxiliary feedback (*lower panels*) the subject had difficulty directing his effort to the muscle, bringing the motoneuron to threshold only transiently during a maximal voluntary attempt (3 spikes generated).

but was unable to *sustain* the appropriate voluntary command for a prolonged period without feedback. Such a result is not unexpected, considering the reported importance of visual feedback in the motor control of deafferented patients (Rothwell *et al.*, 1982; Sanes *et al.*, 1985; Cole *et al.*, 1986). Subjects were commonly unaware whether their attempted contractions had been successful when auditory or visual feedback was removed before a voluntary attempt began. The motoneuron in fig. 6 could be activated in the

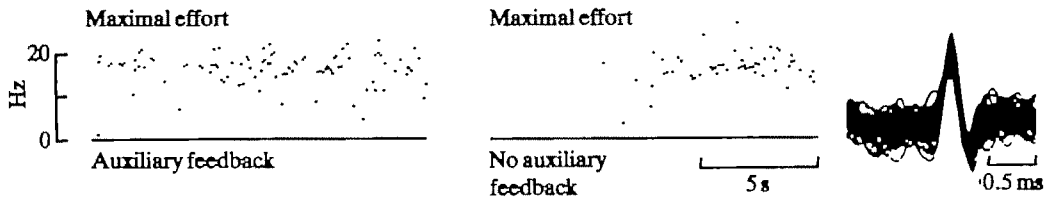


FIG. 6. Behaviour of a motor axon (same as in fig. 4) during maximal voluntary efforts with and without audiovisual feedback. When auxiliary feedback was withdrawn before the second attempt, the recruitment was delayed but the subject could still develop the high discharge frequencies generated when provided with optimal feedback. Superimposed spikes are from the second attempt.

absence of auxiliary feedback but often its recruitment was delayed, and although in this episode the subject could maintain the discharge, the effort eventually resulted in the coactivation of forearm muscles and the injection of distant EMG activity into the recording, that is, the subject lost the ability to 'focus' on the relevant muscle.

When auxiliary feedback was withdrawn *during* an attempted contraction there was often difficulty in maintaining the previously generated motor commands. The discharge became particularly irregular for the motoneuron in fig. 6. On other occasions, however, the sudden withdrawal of feedback did not influence the regularity of the motor discharge. Subjects always reported directing their attention to the relevant muscle and the digit which it usually moved—they neither reported, nor attempted strong ballistic efforts involving remote muscles in the hand or forearm.

Importance of cutaneous feedback

Clearly, any tonic influence provided by low-threshold cutaneous afferents was not essential for subjects to activate motoneurons supplying the intrinsic muscles of the hand: in the position of rest there is little spontaneous activity in cutaneous and joint receptors of the human hand (Knibestöl and Vallbo, 1970; Burke *et al.*, 1988b). Furthermore, the 3 motoneurons innervating muscles acting on digit V, which was completely anaesthetic, were activated by weak efforts (i.e., at low threshold; fig. 3A). However, there is much indirect evidence that the local cutaneous innervation is important in the ability to control the movement of a digit (e.g., Marsden *et al.*, 1972, 1977; Gandevia and McCloskey, 1977b, c), particularly in the fine control of forces during precision grip (Kanda and Desmedt, 1983; Johansson and Westling, 1987; Westling and Johansson, 1987).

The influence of cutaneous feedback via the median nerve on voluntary activation of a denervated muscle was examined in 4 experiments in 3 subjects. Multiunit neural activity was recorded from 2 fascicles supplying first dorsal interosseous, and 1 each innervating

adductor pollicis and the third lumbrical, during attempted contractions of the target muscle. The amplitude of the integrated neural activity was compared when specific cutaneous feedback was or was not provided. The feedback was provided either by the experimenter applying tactile stimulation to the relevant digits. In each of 14 test sequences cutaneous stimulation increased the motor drive to the paralysed muscle during attempted contractions. The mean facilitation was 59% (SE 12%; $P < 0.001$, paired *t* test). This influence is illustrated in fig. 7A and B. Multiunit motor activity directed to first dorsal interosseous increased when the tips of the thumb and index finger were allowed to touch (fig. 7A), and decreased when cutaneous feedback was withdrawn (fig. 7B). Fig. 7C illustrates the facilitatory influence of low-threshold cutaneous afferents on a single motoneuron supplying adductor pollicis; when the tips of the 2 digits were passively separated, the subject had difficulty recruiting the motoneuron. Subjects generally reported that the cutaneous feedback provided a 'reference' to which they were better able to focus their attempts to move the immobile digit.

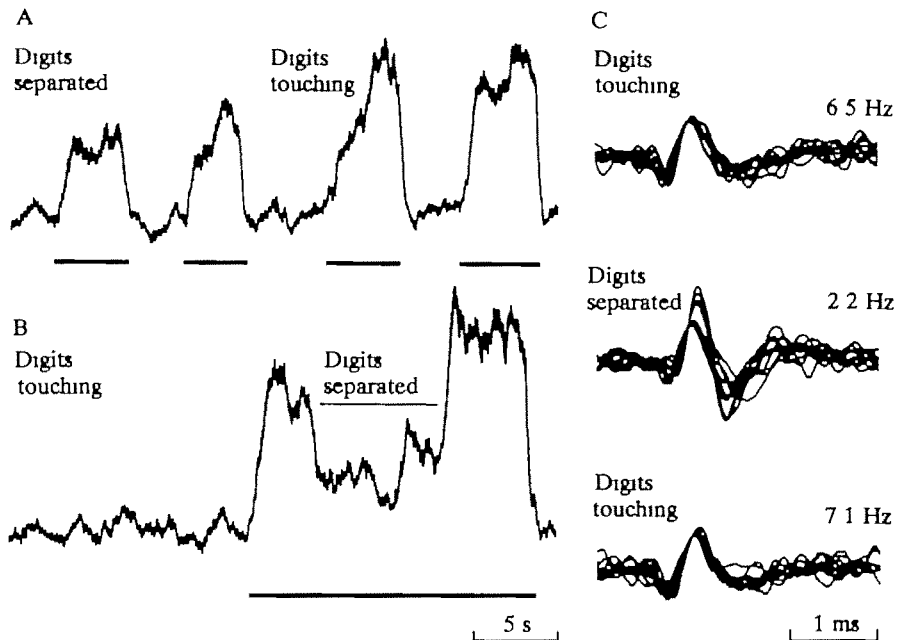


FIG. 7. Influence of tonic activity in cutaneous afferents from the tips of the thumb and index finger on attempts to oppose the immobile digits. Integrated multiunit activity from the fascicle supplying first dorsal interosseous is shown in panels A and B, in which the subject was requested to exert a constant amount of effort (indicated by the thick horizontal lines) and the experimenter either prevented the thumb and index finger from touching or brought them together. In A the motor output during constant efforts was increased in the 2 attempts in which cutaneous feedback was provided; in B the motor output during an 18 s effort was reduced when cutaneous feedback was suddenly withdrawn for 8 s. C, cutaneous facilitation of a motoneuron supplying adductor pollicis. Each set of traces consists of 10 superimposed sweeps. When the tips of the thumb and index were touching (upper and lower records) the subject could activate the motoneuron and sustain a steady discharge at 6.5 Hz (upper records) and 7.1 Hz (lower records). When the tips were separated (middle records) the subject had difficulty recruiting the motoneuron; sporadic spikes were generated at 2.2 Hz and a previously silent motoneuron was recruited.

Ability to grade motoneuron discharge

Using a contralateral matching task, the ability to grade motor activity without feedback was examined for 6 motoneurons, 2 each supplying the third and fourth palmar interosseous and 1 each adductor pollicis and the third lumbrical. The subject attempted to produce a simultaneous effort of the paralysed muscle to match that of the homologous contralateral muscle (*see* fig. 2). A typical sequence in which the subject was able to grade the discharge frequency of the motoneuron with the force on the contralateral side is shown in fig. 8A. The subject could also sustain a particular level of activity (fig. 8B). This indicates that muscle afferent feedback is not essential for grading and sustaining the motor effort. The capacity did not depend on the presence of auxiliary feedback, as shown for those motoneurons that could be activated when auditory or visual feedback was withdrawn.

The matching paradigm also allowed the recruitment thresholds of these 6 motoneurons to be documented objectively. All were activated at levels less than 10% of the maximal voluntary effort (i.e., as assessed from the contralateral matched contraction). The majority

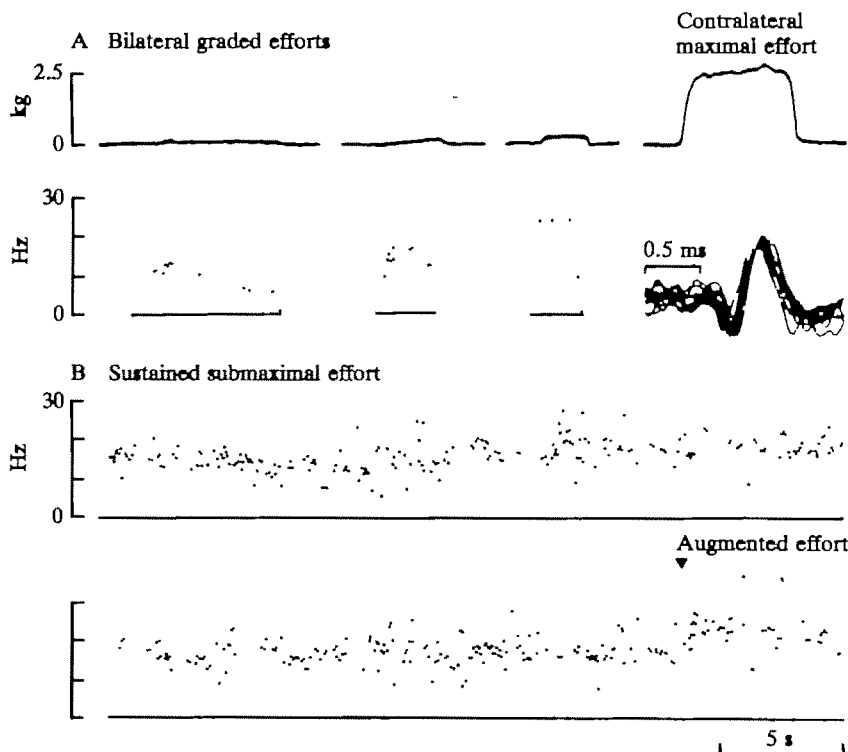


FIG. 8. A, gradation of discharge frequency of a motoneuron supplying adductor pollicis (same as in fig. 7c) during bilateral efforts. Contralateral effort recorded during thumb adduction against a strain gauge. Force generated during contralateral effort provides a reference for the determination of recruitment threshold of the motoneuron. Superimposed spikes recorded during a submaximal effort. B, same motoneuron during an attempt to sustain a constant level of discharge. Upper and lower panels continuous. Towards the end of the attempt the subject was instructed to increase his effort. Note the pronounced discharge irregularity. The overall coefficient of variation prior to the augmented effort was 0.66, during the augmented effort it was 0.56.

of the 16 identified motor axons were of low threshold. Two motoneurons that were considered high threshold were probably activated at levels below 20% of the maximal effort.

For many motoneurons the apparent range over which gradation of discharge could occur was small, such that the mean frequencies generated during maximal efforts were only slightly higher than those generated during submaximal efforts. This occurred for the motor axon depicted in figs 4 and 6; the frequencies developed during weak (fig. 4) and maximal (fig. 6) efforts were similar.

Motoneuron discharge frequencies during maximal voluntary efforts in the absence and presence of muscle afferent feedback

In 2 subjects motoneuron discharge frequencies were recorded during attempted maximal efforts *in the absence* of muscle afferent feedback. Fourteen such efforts of 5–30 s duration were obtained during the recordings from 7 motor axons: 2 supplying first dorsal interosseous, 2 the third palmar interosseous (*see* fig. 6), 2 the third lumbrical and 1 the fourth palmar interosseous. Cutaneous feedback was provided to all except the latter motor axon. The discharge frequencies generated during the efforts were compared with those sampled from individual *motor units* recorded from a normally-innervated first dorsal interosseous muscle in a separate series of experiments, i.e., *in the presence* of muscle afferent feedback (*see* Methods). Motor unit EMG potentials were recorded from an insulated tungsten microelectrode inserted into the muscle during maximal isometric contractions against a strain gauge, each lasting 30 s. Brief trains of single motor unit or muscle fibre EMG potentials (range: 5–111 spikes per train; mean $\pm$ SE: 14 ± 1) were sampled at different times during the slow passage of the highly selective microelectrode through the contracting muscle (Bigland-Ritchie *et al.*, 1983, 1986b; Woods *et al.*, 1987). An example of a motor unit spike train recorded during a maximal voluntary contraction is given in the inset of fig. 10A.

The motor axon and motor unit data for one subject are presented in time-interval histograms and cumulative-probability distributions in fig. 9. The histograms are plotted in 4 ms bins from 8 to 200 ms, which exclude the short intervals associated with 'spike doublets' and a small proportion of long intervals occurring well outside the shoulder region of the histograms. The motor axon data were obtained from 5 axons during 12 maximal voluntary efforts lasting 20–30 s. The motor unit data were obtained from 32 spike trains sampled during 11 maximal voluntary contractions. The histogram for the deafferented motor axons is shifted towards longer interspike intervals (i.e., lower discharge frequencies) relative to that for the motor unit data. The mean discharge frequencies of the motor units and motor axons were 17.2 ± 0.9 (SE) Hz and 12.3 ± 0.9 Hz, respectively ($P = 0.003$, Mann-Whitney U test); the modal interspike intervals correspond to frequencies of 29 Hz and 14 Hz. The disparity would be even greater if the analysis were based on only the initial 10 s period of the prolonged efforts, as motor unit firing rates decline significantly after 10 s (*see below*). In the second subject the maximal efforts lasted only 5–10 s; the mean discharge frequencies generated by the 6 motor units and 2 motor axons were 29.3 ± 2.9 Hz and 16.0 ± 0.3 Hz respectively ($P = 0.023$, Mann-Whitney U test). Thus in the absence of muscle afferent feedback (motor axon data) the motoneurons supplying intrinsic muscles of the hand did not reach the high discharge frequencies achieved by those in receipt of muscle afferent feedback.

It is evident from the wide peaks in the histograms of fig. 9 that, both in the presence and the absence of muscle afferent feedback, the discharge frequencies were irregular (*see also* figs 6, 8B). This irregularity was quantified in terms of the coefficient of variation. When determined from all intervals between 8 and 200 ms, the coefficients of variation for the motor units and motor axons were 0.57 ± 0.03 (SE) and 0.41 ± 0.04 , respectively, during maximal efforts in the 2 subjects referred to above. The difference in variability was statistically significant, but because the motor unit data were obtained from brief spike trains whereas the motor axon data were obtained from long trains, this difference could be artificially large. The coefficient of variation for the motor unit data of all four subjects was 0.52 ± 0.03 . The calculated variabilities were not significantly reduced by excluding intervals greater than 100 ms.

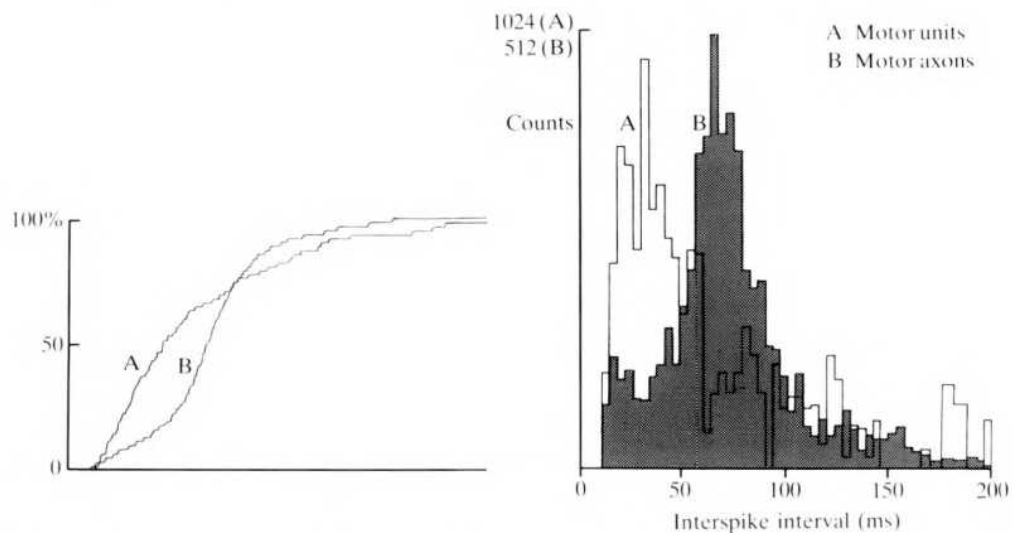


FIG. 9. Distribution of interspike intervals for (A) the motor unit data (muscle afferents intact) and (B) motor axon data (muscle deafferented) of one subject during maximal voluntary efforts. Intervals < 8 ms and > 200 ms are excluded. Distributions are expressed as cumulative probabilities (*left panel*) and time interval histograms (*right panel*). Motoneuron discharge frequencies are lower in the absence of muscle afferent feedback (shaded histogram). Ordinate scales are different for A and B.

Sustained maximal efforts

Multiunit activity of motor axons was recorded in 4 subjects attempting to activate a paralysed and deafferented muscle maximally, to determine whether the progressive reduction in output from the motoneuron pool during sustained maximal efforts was due to peripheral mechanisms (Bigland-Ritchie *et al.*, 1983, 1986b; Bigland-Ritchie and Woods, 1984; Hagbarth *et al.*, 1986; Kukulka *et al.*, 1986; Woods *et al.*, 1987; Garland *et al.*, 1988). Twenty-two sustained maximal attempts lasting 23 ± 2 s (mean $\pm$ SE) were recorded from 3 fascicles supplying first dorsal interosseous, 2 the third palmar interosseous, and 1 each innervating the third lumbrical and the fourth palmar interosseous. Compared with the initial 5 s of the sustained efforts the mean amplitude of the integrated neural activity

in the final 5 s was 102% (SE 6%), that is, there was no reduction in motor output in the absence of feedback from the target muscle.

The progressive decline in motoneuron discharge frequencies during sustained maximal efforts (Bigland-Ritchie *et al.*, 1983, 1986b; Woods *et al.*, 1987) was examined by analysing the motor-unit spike train data from the 4 subjects in 5 s epochs. The mean frequency at the beginning of the 30 s contraction fell from 21.2 ± 1.6 (SE) Hz to 13.0 ± 0.5 Hz at the end. The relative decline in mean frequency is illustrated in fig. 10A. The reduction was significant at the 10–15 s sampling epoch ($P = 0.005$, Mann-Whitney U test). In 1 subject the activities of 5 single motor axons could be followed during sustained efforts of 20–30 s duration (same subject as in fig. 9). Fig. 10B illustrates the relative changes in the discharge frequencies of motor axons (open symbols) and motor units (closed symbols) with time for this subject, for which the data of fig. 9 were reanalysed in 5 s epochs. In the absence of muscle afferent feedback discharge frequencies were maintained for the duration of the efforts (20–30 s). When measured between 5 and 30 s the difference between the two curves was statistically significant ($P = 0.01$, paired t-test).

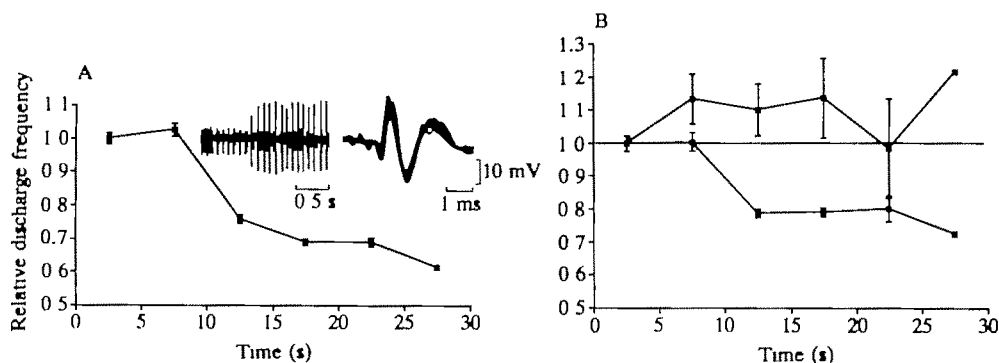


FIG. 10. A, sequential analysis of motor unit discharge frequencies during maximal voluntary efforts of 20–30 s duration; data from 4 subjects expressed in relative terms (mean $\pm$ SE). Spike trains recorded from motor units were analysed in 5 s epochs. Note the decline in motor unit discharge frequencies 10–15 s after the commencement of a maximal voluntary contraction. Inset, motor unit spike train recorded from first dorsal interosseous 15 s after the commencement of a maximal voluntary contraction. During its passage through the contracting muscle the microelectrode approached a large amplitude motor unit; this particular spike train consisted of 27 impulses, the superimposed action potentials of which are illustrated on the right. B, sequential analysis of the motor axon (open symbols) and motor unit (closed symbols) data of fig. 9 (1 subject). There was no progressive decline in discharge frequency of the deafferented motor axons.

DISCUSSION

The present study has employed microneurographic techniques to examine the discharge behaviour of human motor axons during acute deafferentation of the target muscles. Observations on 16 identified motor axons led to the conclusion that information from intramuscular receptors is not essential for the controlled activation of motor units in the intrinsic muscles of the hand. In the complete absence of feedback from the target

muscles subjects can recruit individual motoneurons, grade their activity and sustain a particular level of activity.

Methodological considerations

There have been two previous microneurographic studies of presumed motor axons in conscious human subjects, but both suffered from important methodological limitations. Because any motor act will increase afferent activity from intramuscular, cutaneous and possibly articular receptors, it is impossible to record the activity of motor axons with confidence unless the activity from sensory axons is excluded. In a short report, Freyschuss and Knutsson (1971) recorded from presumed efferent axons during the neuromuscular block induced by succinylcholine. They noted that motor axons in the median and ulnar nerves displayed relatively low levels of activity, even during maximal attempts to contract the paralysed muscles, but suggested that succinylcholine may have influenced the excitability of the motoneurons indirectly. Recently, Ribot *et al.* (1986) detailed the behaviour of 12 axons in the common peroneal nerve which were classified as motor axons because they could not be activated by mechanical stimuli. This qualitative study provided no information on the discharge frequencies or discharge regularity of the 6 axons considered 'skeletomotor', classified as such because of their quiescence when the target muscle was completely relaxed.

Neural activity recorded proximal to a complete nerve block must be efferent, and the microneurographic technique favours recording from large-diameter alpha motor axons. Anaesthetic block of ulnar nerve at the wrist offers a particular advantage in the study of motoneuron behaviour: in the radial aspect of the hand the intrinsic muscles that receive ulnar innervation are completely paralysed and anaesthetic, but cutaneous and much articular information from the digits on which the muscles act is intact via the median nerve. The method therefore allows motoneuron behaviour to be studied in the absence of feedback from receptors within the target muscle and synergistic intrinsic muscles.

The present technique has clear advantages over previous studies, but may suffer from a sampling bias. Any motor axons that could not be activated following the removal of muscle afferent inputs would not be identified. Those that could be activated were all of fairly low threshold; the majority would have been recruited at levels <10% of the maximal voluntary effort, perhaps suggesting that type S motor units dominated the sample. Conversely, the motor unit or muscle fibre action potentials recorded during a sustained maximal voluntary contraction need to be large for triggering purposes, suggesting that the sample may be dominated by type FR and FF motor units.

Motoneuron behaviour in the absence of muscle afferent feedback

When requested to recruit a deafferented motoneuron and to grade or sustain its activity, subjects could direct their effort appropriately (see Gandevia and Rothwell, 1987), although some 'auxiliary feedback', in the form of an auditory or visual correlate of the motor attempt, was occasionally necessary. In the absence of such information, subjects could generally recruit a motoneuron, indicating that their efforts were correctly directed towards the relevant muscle, but the ability to sustain a particular level of activity was sometimes lost. Information from low-threshold cutaneous afferents of the digits (via the median nerve) could provide an important facilitatory influence on the motoneurons, as previously demonstrated for single motor units of first dorsal interosseous (Datta and Stephens, 1981;

Garnett and Stephens, 1981; Kanda and Desmedt, 1983). Because simultaneous recordings from 2 motor axons were not made during the complete block, no comments can be made on the reported reversals in recruitment order evoked by cutaneous afferent stimulation (Garnett and Stephens, 1981; Kanda and Desmedt, 1983) and following a reduction in muscle afferent feedback (Grimby and Hannerz, 1976).

At all levels of voluntary drive the discharge frequencies of the motor axons were irregular, but this is not due to errors in triggering from the unitary action potentials (*see* fig. 3). The mean variability was about 40% during maximal efforts. However, the variability of axonal discharge was less than the variability of motor units with intact afferent and efferent innervation during maximal voluntary contractions of first dorsal interosseous. This does not support the postulated capacity of muscle afferents to reduce the discharge irregularities of tonically active motoneurons (Fukushima *et al.*, 1976).

The coefficients of variation for the motor unit data (mean 0.52) are considerably higher than those reported in other studies, but this is likely to be due to the acceptance criteria imposed in those studies. For example, Bigland-Ritchie *et al.* (1983) reported a coefficient of approximately 0.3 for single motor units of adductor pollicis during maximal voluntary contractions, but included only those portions of a spike train with the most regular intervals. In a later study the same group formalized their acceptance criteria—units with interspike intervals exhibiting a standard deviation greater than 15% of the mean frequency were rejected (Woods *et al.*, 1987). Our formal approach was to exclude all intervals less than 8 ms and greater than 200 ms.

Motoneuron discharge frequencies during maximal voluntary efforts were significantly lower in the absence of muscle afferent feedback. It could be argued that the 2 subjects from whom these data were obtained could not maximally activate the motoneuron pool when deprived of peripheral feedback. Both subjects have demonstrated the ability to activate several proximal and distal muscles of the limbs maximally, including the intrinsic muscles of the hand (*see* fig. 3, Gandevia and McKenzie, 1988), and subjects can direct their efforts to single muscles in the hand without relying on afferent information (Gandevia and Rothwell, 1987; *see also below*). However, with current methods it is not possible to *prove* that maximal corticofugal drive was maintained during the attempted maximal contractions of the paralysed muscles.

As mentioned earlier, there may have been sampling bias in the present experiments, such that the disparity in the mean discharge frequencies generated by the *motor axons* and *motor units* during maximal voluntary efforts could reflect differences between low and high-threshold motoneurons respectively. However, there is an alternative explanation. Hagbarth *et al.* (1986) reported that the mean discharge frequencies of tibialis anterior motor units in maximal voluntary contractions are decreased when the peroneal nerve is *partially* blocked by local anaesthetic, presumably affecting gamma motor axons preferentially. This finding suggests a *net* facilitatory influence of muscle spindle afferents onto the homonymous motoneuron pool (Hagbarth *et al.*, 1986). The disparity in mean discharge frequencies in the deafferented and intact conditions indicates the *maximal* amount of facilitation that muscle spindles can provide.

In the absence of muscle afferent feedback there was no progressive reduction in the mean amplitude of integrated neural activity during sustained maximal voluntary efforts, and the discharge frequencies of single motoneurons did not decline. In support of previous evidence (Kukulka *et al.*, 1986; Woods *et al.*, 1987; Garland *et al.*, 1988), this suggests

that the reduction in motoneuron discharge frequencies during fatiguing contractions is of peripheral origin. This progressive decline of motor unit discharge frequencies also occurs during prolonged submaximal contractions (Bigland-Ritchie *et al.*, 1986a), and may be due to progressive reflex inhibition mediated by small-diameter muscle afferents, as argued by Bigland-Ritchie and her colleagues (Bigland-Ritchie and Woods, 1984; Bigland-Ritchie *et al.*, 1983, 1986b; Woods *et al.*, 1987), and/or to a progressive disfacilitation of the motoneuron pool due to a waning of fusimotor-mediated spindle excitation (Bongiovanni and Hagbarth, 1990). Indeed, it seems probable that the latter mechanism would contribute more than the former during the initial seconds of a sustained contraction, whereas the metabolically-induced inhibition would become effective late in the contraction.

Relevance to studies of patients with sensory deficits

Motor control in patients with sensory neuropathies, involving large-diameter muscle, cutaneous and articular afferents, has been studied at the metacarpophalangeal joint (Rothwell *et al.*, 1982), wrist (Sanes *et al.*, 1985) and elbow (Forget and Lamarre, 1987). The manual motor capabilities of a hemianaesthetic patient, in whom the contralateral somatosensory cortex was infarcted, have also been examined (Jeannerod *et al.*, 1984; *see also* Volpe *et al.*, 1979). In addition to the inaccuracies of movement in the absence of visual guidance of their performance, a common difficulty for these deafferented patients was inability to maintain a constant position or level of force, although some long-term improvement in the latter may possibly develop (*see* Cole, 1987). Excessive muscle cocontraction may contribute to the difficulty in performing complex coordinated multiarticular movements, although simple repetitive alternating movements may be minimally affected. Some stereotyped learned motor behaviours are largely unaffected in the deafferented patients (Volpe *et al.*, 1979; Rothwell *et al.*, 1982; *see also* Polit and Bizzi, 1979). For example, the ability to generate the triphasic EMG pattern of agonist-antagonist pairs in ballistic contractions is retained in the absence of peripheral feedback, although the timing and magnitudes of the components are upset (Rothwell *et al.*, 1982; Sanes *et al.*, 1985; Forget and Lamarre, 1987).

Cutaneous afferent information is important in the fine control of hand movements (Rothwell *et al.*, 1982; Johansson and Westling, 1984, 1987; Brink and Mackel, 1987). Information from low-threshold cutaneous afferents may be important for the hand through at least two mechanisms: provision of a 'reference signal' that a motor task has occurred, and provision of facilitation to relevant motoneuron pools. Deficits in motor performance following deafferentation will occur through both these mechanisms. The former will contribute more to deficits in the complex sequencing of (novel) movements, but cutaneous facilitation may be more important for sustaining the motor activity of a single set of muscles.

The present observations of motoneuron behaviour in the absence of *muscle* afferent feedback require some reinterpretation of the results from deafferented patients. The recruitment of motoneurons and the fractionation of effort do not require a constant synaptic input from the periphery to the spinal motoneurons or to the sensorimotor cortex. Furthermore, in contrast to the conclusions of Rothwell *et al.* (1982) and Sanes *et al.* (1985), the generation of a constant level of force does not depend on peripheral feedback, specifically the facilitatory influence provided by muscle spindles (Rothwell *et al.*, 1982),

as indicated by the ability of the acutely deafferented motoneurons to sustain a constant level of discharge. Subjects may require auditory or visual feedback, but these cues are unlikely to be translated into a descending synaptic drive to spinal motoneurons; such auxiliary feedback probably provides only a reference signal, indicating to the subject that the centrally generated command was sufficient to drive the motoneuron. Chronically deafferented patients can grade their central commands (Rothwell *et al.*, 1982; Sanes *et al.*, 1985; Cole, 1987), as could the acutely deafferented subjects in the present study. Furthermore, normal subjects can judge forces accurately with only a minimal afferent signal that the motor command has been successful in generating the appropriate force (Gandevia and McCloskey, 1978).

In conclusion, our studies demonstrate that subjects can direct the central neural machinery for generating *simple* motor tasks independent of peripheral feedback. The sequencing and execution of *complex* manual movements may well be more limited in the absence of feedback from intramuscular receptors. For some tasks auxiliary feedback may be required, both by normal subjects with a limited acute deafferentation and by patients with the extensive deafferentation associated with large-fibre sensory neuropathy.

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BOOK REVIEWS

Recollections of my Life. By Santiago Ramón y Cajal. Translated by E. Horne Craigie with Juan Cano. Foreword by W. Maxwell Cowan. 1989. Pp. 638. London and Cambridge, MA: MIT Press. Price \$22.95 (paperback).

This book compiles two of Cajal's autobiographical works: *My Childhood and Youth* and *Story of my Scientific Work*. It is an invaluable source of information on the personality of Cajal, his life and scientific career, opinions about the world in his time, his relationship with foreign colleagues, and his multiple passions: science, philosophy, photography, literature. The foreword to this paperback edition by W. M. Cowan is informative and overcome with admiration for the figure of Cajal.

As it happens with many great thinkers, the scientific stature of Ramón y Cajal grows with the passage of time. To an important extent, this relates to the fact that most of his findings and ideas continuously appreciate as they are confirmed by contemporary work performed with the advantage of new technologies. Today, the theory that won Nobel laurels for Ramón y Cajal, *The Doctrine of the Neuron*, is a basic working reality for neuroscientists, while attention shifts towards *Degeneration and Regeneration of the Nervous System* (Oxford University Press, 1928, translated into English by R. M. May), a subject of current incandescence in the context of neuronal plasticity and cerebral transplants, or towards histology of the cerebral cortex, a Grail in the context of dementias (*Cajal on the Cerebral Cortex* — an annotated translation of the complete writings by Javier DeFelipe and Edward G. Jones. New York: Oxford University Press, 1988).

In this regard, it is a frustration that Cajal's opus magnum, *Histologie du Système Nerveux* (Maloine, Paris, 1911), has not been translated into English. The French edition, re-edited in Spain by the High Council of Scientific Investigations in 1952, has been out of print for many years. Death prevented Cajal from finishing a new edition in which he intended to incorporate a vast amount of new graphic and photographic material and which remains unpublished.

The English translation of *Recollections of my Life* does adequately capture the Spanish version, a difficult task, when it is realised that the author's Spanish, often baroque and convoluted, does not lend itself to easy translation. It is a pity that the English reader will not be able to enjoy the vast number of dazzling illustrations and drawings that make almost one-third of the second part of the Spanish version (*Recuerdos de mi Vida: Historia de mi Labor Científica*. Madrid: Alianza Universidad, 1981). But as the translators comment in the preface, it would have made the book excessively large.

In the presentation of the Spanish edition of *Recollections of my Life*, Severo Ochoa, the Spanish Nobel laureate stated: 'The reading and re-reading *Recollections of my Life* and *Rules and Advice on Scientific Research* compelled me to devote my life to biological research.'

In its joyful faith in the human being and scientific research, the revival by MIT Press of this entertaining book, which has been out of print for so long, is a spiritual gift to the multiple fans of Ramón y Cajal.

JOSÉ M. FERNANDEZ AND JOSÉ OCHOA

Parkinson's Disease, Edited by Gerald Stern. 1990. Pp. 688. London: Chapman and Hall. Price £79.00.

In this book the editor has assembled a team of 41 international experts to give a comprehensive overview of this subject. The book is divided into 3 main sections: neuroscience, clinical considerations, and treatment, and also includes a short historical account of the life of James Parkinson. The neuroscience section is particularly well written. There is a detailed, readable account of the functional anatomy of the basal ganglia by Keith Webster which any nonspecialist can follow. An important omission from this chapter, however, is the evidence now available for an excitatory glutamatergic pathway connecting subthalamus to internal pallidum. Lesioning this pathway has recently been shown to cure rigidity in MPTP-treated primates.

David Marsden has written an excellent chapter on the neurophysiology, Yves Agid on the biochemistry of Parkinson's disease (PD), and Edmund Rolls reviews the role of the basal ganglia in cognitive function. The chapter on the importance of the Lewy body in the pathology of PD suffers from the lack of inclusion of any of the recent ubiquitin-staining data now available. As a consequence the distribution of Lewy body pathology is underestimated and the important relationship between cortical Lewy body disease and Parkinson's disease is only briefly reviewed.

The clinical section is thorough but there is a degree of overlap of the chapter contents by the various contributors. A long chapter on the clinical features of PD suffers from lack of pathological validation: it is not clear to the reader, for example, whether the rapidly progressive, poorly L-dopa-responsive, akinetic-rigid variant of PD described by this author, or the occasional presence of downgaze paresis which he claims can be present, represent part of the clinical spectrum of Lewy body nigral degeneration, or atypical pathology. Particularly enjoyable chapters were those on differential diagnosis by Roger Duvoisin, and behavioural neurology by Andrew Lees. The assessment and measurement chapter provides a detailed comparison of the various rating scales for PD, but the reader is left a little unclear as to which scales the author personally recommends.

The treatment section is also well written. One wonders whether in the light of the Deprenyl DATATOP study Melvin Yahr would still hold to his scheme of treating early PD with reassurance in his chapter on Principles of medical treatment, rather than proceeding directly to the use of anticholinergics and L-Deprenyl. The role of the various dopamine agonists in PD is exhaustively discussed by the New York University School of Medicine group, and lisuride appears to emerge as most useful. There are chapters on both levodopa-induced dyskinesias and motor fluctuations, the mechanisms of which still appear to be imperfectly understood. Unfortunately no chapters on the results of using apomorphine infusions, or the outcome of fetal transplantations are included in this volume. There is an interesting chapter by Hiroto Narabayashi on the role of stereotactic surgery in PD, convincingly demonstrating its effectiveness for controlling refractory tremor.

In summary, I thoroughly enjoyed reading this collection of chapters and learnt a great deal about both PD and basal ganglia function. It is an easy work for the nonspecialist to assimilate, and could also be appreciated by patients suffering from PD. The editor is to be congratulated.

DAVID BROOKS

Drugs for the Treatment of Parkinson's Disease, Handbook of Experimental Pharmacology, Volume 88. Edited by D. B. Calne. 1989. Pp. 599. Berlin: Springer. Price DM 480 00

Function and Dysfunction in the Basal Ganglia. Edited by A. J. Franks, J. W. Ironside, R. H. S. Mindham, R. J. Smith, E. G. S. Spokes and W. W. Winlow. 1990. Pp. 277. Manchester: Manchester University Press. Price £49.95.

The therapeutics of Parkinson's disease is an increasingly entangled and controversial field. Although levodopa remains the most effective remedy, concern lingers with regard to its long-term safety and debate rages on precisely how and when it should be administered. For example, should it be given early in the course of the disease or held back for as long as possible; should it be given in maximum tolerated doses or restricted to a maximum daily dose of 400 mg? Can a better deal for the patient be achieved by combining levodopa at the beginning of medical treatment with the selective monoamine oxidase inhibitor selegiline (Deprenyl), and/or a dopamine receptor agonist drug? Novel drug delivery systems, including continuous subcutaneous administration of apomorphine by ambulatory minipump, transdermal application of PHNO by skin patch and levodopa methyl ester by gastric pouch, have now also entered the therapeutic arena and the first convincing improvement from a fetal putaminal implant is now on record. It seems clear that the management of Parkinson's disease will be a highly skilled labour-intensive discipline before the end of the millennium. In Donald Calne's book all these approaches are tackled with scholarly and critical accounts by internationally respected physicians. The chapters flow logically from the exciting possibility of preventative treatment through the old standbys of anticholinergics and amantadine to 2 excellent chapters on levodopa by Le Witt and Fahn. Adjuvant therapies follow with chapters on selective monoamine oxidase inhibition therapy followed by a parade of different dopamine receptor agonist drugs to the final

chapter on experimental implantation procedures. These chapters, which are the framework of the book, provide a comprehensive and international view of available drugs. Selegiline has only just become available in the United States and the useful peripheral dopamine receptor antagonist discussed by David Parkes is still fighting its way through the F.D.A. Lisuride is not available in the United States and pergolide is not yet available in Europe. Furthermore, most of the drugs mentioned in this account are not available, because of their cost, to most of the Third World and it is a pity that a chapter on herbal sources of anti-parkinsonian drugs was not included, particularly as plants have played such a crucial role in therapeutic progress in this area. The book could also have been strengthened by two or three personal contrasting accounts by respected physicians to illustrate the dichotomy of contemporary views on how best to use the available treatments. The first 8 chapters of the book address pathology, aetiology and neurophysiology of Parkinson's disease and there are the inevitable sections on neuroimaging with PET and on MPTP. Clearly an introductory section on what we know about Parkinson's disease and how it is diagnosed is essential in a therapeutic textbook of this sort, but the prolix and in some cases idiosyncratic views provided here are inappropriate. If read from cover to cover this book is likely to leave many readers with a tension headache. As a reference book it can be recommended for the comprehensiveness and authority of many of its core chapters.

The Function and Dysfunction of the Basal Ganglia is the edited proceedings of a 4 day international symposium held at the University of Leeds in 1987. The contributors to the book, who represent only a sprinkling of those who presented papers at the meeting, provide a pleasing cocktail of Johns Hopkins booch with an improbable red and white rose bouquet. An exemplary account of the anatomy of 5 thalamo-cortical circuits is given in the introductory chapter by DeLong, which more than fulfils the aims of the book to provide an intelligible fusion of currently available concepts on the function of the basal ganglia in jargon-free English. As always with DeLong's writings, the accompanying drawings and figures are models of clarity, reinforcing the text. Each of the 5 circuitries project multiple, partly overlapping inputs from several anatomically and functionally related cortical areas onto a specific portion of the striatum which is then directed onwards to specific areas of the internal segment of the globus pallidus and zona reticulata of the substantia nigra and finally onto subregions of the thalamus. Each loop is then closed by thalamic projections to one of the original cortical areas. After processing and integrating a number of functionally related cortical areas in the basal ganglia, funnelling occurs by means of closed loops back to one specific cortical region. DeLong sees the basal ganglia as an important crossroads for the understanding of neurological and psychiatric disease and discusses the motor, cognitive and affective functions. In the epilogue to the book Dr McHugh discusses dyskinesias, dementia and depression as basal ganglia symptoms explicable on the basis of the independent loop systems. He also provides some sage aphorisms relating to the blind spots and mirages inherent in neuroscientific methods and the problems of interdisciplinary collaboration. The rest of the book is unfortunately a disparate medley with the eloquent neurological poetry of Stern and the impressive autoradiographic studies of Crossman rubbing shoulders uneasily with wet dog shakes and Straub tails of rats and the human astrocytoma clone D384. In a book of this size, 2 chapters on transplants in MPTP-treated monkeys seems profligate. I preferred the mandatory articles on neuroimaging and MPTP in this volume to those in Calne's book. Nevertheless, while being well written, both had a slightly faded, jaded impact, partly as a result of the intolerable over-exposure of these rapidly developing areas by repetitive reviews. Although dopamine receptor subtypes now seem to have contracted from 5 to 2, Coward and Markstein in an excellent short chapter show that far from simplifying matters the inter-reaction between D1 and D2 receptors is extremely complex and the role of the D1 receptor in the human brain remains obscure. The book contains 4 clinical chapters on cognitive aspects of basal ganglia disease, all of which are highly specialized but of interest, and I greatly enjoyed 2 speculative chapters on the role of the basal ganglia in depression and schizophrenia. This book is easy to read, concise and contains a few pearls. Despite its noble aspirations, however, it does not sustain the quality or breadth of the proceedings of a CIBA symposium; the presentations are uneven, over-specialized and at times frankly quirky.

ANDREW LEES

Seizures and Epilepsy. By Jerome Engel, Jr. *Contemporary Neurology Series*, Volume 31. 1989. Pp. 536. F. A. Davis. Price £61.88.

Seizure Recognition and Treatment. By Richard Lechtenberg. 1990. Pp. 198. Edinburgh: Churchill Livingstone. Price £29.95.

There is now a veritable plethora of books available on epilepsy and the reader could easily be forgiven for questioning the necessity for two more on the subject. However, both these single author books originating from the United States are worthwhile and each is likely to find its own niche as a standard work. Where they both score highly is as single author texts with a consistency of approach that is often lacking in many of the multiauthor texts currently available in the field of epilepsy, most of which are derived from the proceedings of various international symposia.

Engel's approach (*Seizures and Epilepsy*), is comprehensive and academic. The starting point is the description of the cellular mechanisms of neuronal excitation and the abnormalities that underlie epilepsy. From this point clinical themes are developed, including the classification of seizures and epilepsy syndromes, the aetiology of epilepsy and the processes leading to epileptogenesis. The broader concepts of management are then discussed. The text is fully referenced and the areas of controversy are relatively fully discussed. While Engel acknowledges the contributions and criticisms of a number of individuals with an international reputation in varied aspects of epilepsy, one can nevertheless only marvel at the amount of work and the broad intellectual grasp that was necessary to produce this work, covering as it does every aspect from micro-electrode studies of single cells in the laboratory to aspects of psychosocial management of patients in the clinic. It is difficult to envisage a better in-depth discussion for someone wanting to read about epilepsy and to have this range of aspects discussed in a uniform and coherent manner.

By contrast, Lechtenberg's book (*Seizure Recognition and Treatment*), is a practical text that adopts a common-sense approach on how to manage people with epilepsy. Referencing is limited to essential articles and reviews, and one immediately gains the impression that the author is writing from a considerable personal experience of caring for people with epilepsy. The book begins by emphasizing the clinical differences between acute symptomatic seizures and epilepsy. It deals in a practical way with the value and limitations of investigational techniques in diagnosing epilepsy. There is a common-sense approach to the classification of seizures and epilepsies and an excellent description of the differential diagnosis of epileptic seizures with the striking exception that syncope does not come in for a mention. The second half of the book deals with approaches to management for the patient with epilepsy and the psychosocial complications of epilepsy are well dealt with. Here then is a practical, clinical approach to epilepsy that will recommend itself to any general physician or neurologist in training who is looking for a well-written, easy to read, didactic approach to the management of people with seizures and epilepsy.

DAVID CHADWICK

Neurological Emergencies. By S. D. Shorvon. 1989. Pp. 108. Guildford: Butterworths. Price £5.95 (paperback).

This short text addresses in 100 pages an important area of medical practice. It sets out to be an essential practical guide to the diagnosis and management of the acute neurological emergency. The content and presentation is relevant to the casualty officer and house officer rather than to the neurologist or neurosurgeon in training.

Ten topics are covered, with a major emphasis on coma, infection, stroke and vascular syndromes, head injury, acute spinal cord dysfunction and respiratory failure. There is reliance on lists of conditions in differential diagnosis, which is understandable since this is a convenient way of comprehensive ready reference and has the advantage of overall completeness. An innate disadvantage, however, is a tendency to distraction from in-depth analysis of the truly common conditions which present difficulty and uncertainty to the relatively inexperienced doctor in an emergency situation. The important subject of status epilepticus is particularly well covered, and can be recommended as a clear and didactic guide to management. Similarly, meningitis is treated in a concise and secure manner without ambiguity.

The section on coma illustrates the dilemma of how much can be reviewed in a text of this nature, and how much can be left out. It is essential to indicate the relevance of EEG, CT scanning and CSF examination. However, in the emergency situation there must always be a clear distinction between the differential thought process and responsibilities of a neurological team against those of the primary receiving doctor. He must know precisely what, and precisely when to refer.

In analysing possible causes of coma the list is exhaustive. One must agree that classification is meaningful if nothing is to be missed in an assessment. Nonetheless, a more explicit focus on common emergencies, such as stroke, subarachnoid haemorrhage, raised intracranial pressure, meningitis, metabolic coma, and poisoning, with careful clinical descriptions, would concentrate the mind of the young doctor better to the individual case as it presents.

Inevitably there are one or two points which engender educated debate. The place of antihypertensive drugs in acute hypertension associated with subarachnoid haemorrhage or brainstem lesions; the desirability of initiating anticonvulsant treatment with a 1 g loading dose of phenytoin in a comatose patient with a depressed fracture or intracranial haemorrhage; exactly when to perform lumbar puncture in meningitis with papilloedema. These criticisms apart, the author has gathered together common neurological emergencies, and presented the problems they pose precisely, simply and lucidly. The subject is an important one, and the principles set out in this book should lead to further critical appraisal of this problematical area.

The difficulty in laying down sharp guidelines, and this is appreciated by the author, is that there is much variation in the ease of access to neurological and neurosurgical services and guidance in many district general hospitals. It is in this situation that this small practical manual is recommended, to be read in association with other larger texts as a reliable guide to a young doctor who has to face this highly anxious area of the neurological emergency.

J. R. HERON

A Colour Atlas of Brain Disorders in the Newborn. By L. S. de Vries, L. M. S. Dubowitz, V. Dubowitz and J. M. Pennock. 1990. Pp. 199. London: Wolfe Medical. Price £50.00.

This attractive book is the third in a series of atlases from the same publishing house. Its precursors are *A Colour Atlas of Muscle Disorders in Childhood* (Dubowitz) and another of multiple sclerosis (Adams).

An atlas is a useful format for conveying a mass of data on a subject, and lends itself particularly to the presentation of information on neonatal brain disorders. This field has seen spectacular progress in recent years, with which it is difficult to keep up. This new volume, by a team from the Hammersmith Hospital, provides a welcome update, correlating clinical features with the results of imaging by ultrasound, magnetic resonance and CT, with some neurophysiological and neuropathological material.

The introduction deals in detail with ultrasound imaging and clinical evaluation and in less detail with other modalities of investigation (auditory brainstem, visual and somatosensory evoked responses, electroencephalography, Doppler ultrasound and magnetic resonance imaging). The principles of MRI are discussed in Chapter 1, and the remaining 5 chapters deal with the pathological entities of intraventricular and periventricular haemorrhage, leukomalacia, cerebral artery infarction, haemorrhagic and ischaemic lesions of antenatal origin, and hypoxic-ischaemic encephalopathy in the full-term infant.

Fifty case histories are presented, profusely illustrated with clinical photographs, images of various kinds, neurophysiological, Doppler and other studies. The pathology of the brain is illustrated in a few fatal cases. The biographies of these children are thus displayed in a way which seems unique in its detail and vividness. It is difficult to know where one could look for similar material. Standard texts, such as Volpe's *Neurology of the Newborn*, or Diebler and Dulac's *Pediatric Neurology and Neuroradiology*, which remain essential reading for the neonatologist and child neurologist, cannot, by their very nature and the limitations inseparable from a textbook, compete with the approach of this atlas. The colour photographs are superb. I counted 273 of these, mainly clinical. (How can some publishers achieve this *richesse*, while others are so parsimonious of colour?) The book appears to have been produced in Britain and not in Ultima Thule, so that its relatively low price provides another pleasant surprise.

The cases, like all well presented and selected ones, make fascinating reading for the aficionado. Comments on individual or groups of cases emphasize the lessons to be drawn. A particularly interesting comparison is that of premature twins of 27 weeks' gestation, of whom one developed an intraventricular

haemorrhage and the other cystic periventricular leukomalacia. Differences were already evident clinically between the two in the newborn period and were much more marked at seven months of age, when the latter showed the signs of spastic diplegia in evolution while the former appeared to be performing normally.

I think that neonatologists, child neurologists and, indeed, paediatricians in general, need to have access to this useful and attractive book.

E. M. BRETT

The Clinical Neurology of Old Age. Edited by Raymond Tallis. 1989. Pp. 585. Chichester: John Wiley. Price £70.00.

The especial role of a book devoted to the clinical neurology of old age, aside from opening a window on those disorders peculiar to the elderly, must surely be to offer a suitable pathophysiological and psychosocial context for the not uncommonly complex matter of assessment. Some attempt at this is made in an initial section with various generally relevant contributions. They seem, however, to display a certain lack of bite and direction which is epitomized in the somewhat perfunctory handling of the matter of history taking, which is nowhere more important or more taxing than with older patients.

In the handling of individual disease topics, the section on autonomic dysfunction sets an exemplary standard, combining a breadth of generally relevant information with sanguine depth of clinical good sense and direction. Somewhat in contrast is the handling of the very much more important and weighty problems which go under the title of 'dementia'. There is, in particular, no sound guidance upon the assessment and management of normal pressure hydrocephalus which shares this relative neglect with the topic of subdural haematoma.

There is the proper inclusion of sections devoted to the consideration of drug-induced disease and confusional states and there are also generally informative, sound and helpful sections on spinal and cerebrovascular disease.

Some readers may be disappointed that greater use has not been made of the opportunity to examine differential diagnosis and management of some of the more unusual neurological problems of the elderly, such as may occur with the coexistence of severe and symptomatic cervical and lumbar spondylotic disease.

A whole chapter is devoted to the consideration of motor neuron disease, but in view of the suitable recognition of the problems posed, it is, perhaps, all the more disappointing that there is no mention of the occasional early occurrence of respiratory insufficiency for which suitable management may give greater quality to life and also prolong it. Among other disappointing omissions are the lack of any mention of the increasingly diagnosed inclusion body myositis which seems especially to be encountered in the elderly and there is similarly no mention of unusual variants such as substantial motor impairment as a result of a zoster infection.

Discussion of the possible value of neurophysiological examination in the investigation of neuromuscular disease in the elderly is distinctly coy and includes the unusual and somewhat extreme suggestion that it is reasonable to forego formal neurophysiological assessment in those patients for whom a positive Tensilon test has been documented. This suggestion would seem to be doubly dangerous at a time of increasing emphasis on management budgeting, although it might, perhaps, be put in to the suitable context by clinical audit discussion.

With regard to the more immediate aspects of patient evaluation, the somewhat uncritical comment that 'fasciculation is usually a benign symptom' might cause misgivings for some, and the implication in another section that extensor plantar responses might be passed off as an idiopathic feature of old age should also be received with some circumspection.

This is a worthy attempt to cater for the need for a book of this kind, but any future edition would benefit from careful consideration given both to matters of detail and of content. It might be both of interest and value to include a section on the molecular biology of ageing, and a separate section devoted to the patterns of immunological disease, and disturbances of immune function in the elderly would also seem to have an important place.

I would finally suggest that the helpful list of information sources for the disabled should be more readily located and it might also be expanded.

C. J. F. DAVIS

Issues in Pain Measurement. *Advances in Pain Research and Therapy*, Volume 12. Edited by C. Richard Chapman and John D. Loeser. 1989. Pp. 570. New York: Raven Press. Price \$137.50.

Many early reports in the literature of treatments for chronic pain can be rightly criticized on grounds of inadequate pain measurement. About 20 years ago, this led to the development of a variety of pain measures and scales. The relatively simple, but robust visual analogue scales, originally introduced into rheumatological practice, have found wide application. Increasingly sophisticated measures which attempted to provide quantitative information about the affective emotional aspects of pain in addition to straightforward pain severity, were pioneered by Melzack and colleagues. The resulting McGill pain questionnaire introduced in 1975 remains the most widely used scale in clinical practice, providing diagnostically useful information as well as being a reasonably sensitive measure of change in pain severity.

The problems of measurability and practical measurement of pain continue to vex those interested in chronic pain, both in clinical practice and in human and animal research. Psychologists particularly have developed what amounts to a subspeciality devoted to the philosophy, theory and practical aspects of pain measurement. A glance at the pain literature reveals the extent of this interest and industry. Papers reporting different rating scales for different types of chronic pain abound.

The present book, a multiauthor work arising from a three day conference in Seattle in 1988, considers the many continuing controversies concerning which pain measures are valid and useful and the need to try and find some unanimity in an increasingly confused area. As the editors remark in their opening phrase 'Pain measurement is fundamental to progress in multi-disciplinary pain research, but it is a focus of discord within the field'. Not surprisingly, an underlying theme throughout this lengthy book is the difficulty in defining pain adequately. A clear definition is an obvious prerequisite to attempts to measure it. While there is reasonable agreement about general definitions of pain, when it comes to measurement these definitions tend to be too vague, and chronic pain needs to be broken down into at least four major aspects, which include nociception, pain sensation, suffering and pain behaviours. Each aspect may be legitimately measured but in isolation is an insufficient index of the overall experience of chronic pain. Increasingly complex multidimensional pain scales have been developed to cope with this problem.

This book is certainly comprehensive in its coverage of the problems but does not provide us with easy solutions. The opening chapters on philosophy of pain measurement and measurement theory are wide ranging and apply equally to measurement in all scientific experiments. These chapters are followed refreshingly by Sternbach on the linguistic problems in pain measurement. Here is clinical commonsense from an experienced psychologist. Those not familiar with the pain measurement literature would do well to read this chapter first.

Pain measurement in animal experiments is considered next. The central issue here is the validity of inference of pain from simple animal behaviours. The models used have proved useful in understanding pharmacology, but what receives little mention is that the time scale for the great majority of the behaviours observed in such experiments is less than 1 minute. One must question the relevance of such models to chronic pain in animals. These have proved controversial, but seem to have more to offer than most of the acute pain animal tests currently still used by many researchers.

A problem very much linked with the use of animals for acute and chronic pain research and particularly the chronic models such as rat adjuvant arthritis, is the ethical question of subjecting animals to such experiments. This topic is discussed at some length.

Developing the theme of animal research further, there are 4 chapters on the potential for investigating routine painful procedures used in animal husbandry, currently regarded as being quite acceptable from a pain point of view. Procedures such as mulesing, castration, tail docking and electro-immobilization, all done without anaesthetic, are described. These must surely be extremely painful, with recovery from some of the procedures taking place over several days at least. As far as painfulness is concerned, these currently acceptable veterinary operations done on hundreds of thousands of sheep and cattle each year put any of the widely discussed and controversial animal laboratory models in the shade. There is clearly much scope here for pain research, both in large and small veterinary practices. Included in this interesting section of the book, there is a fascinating chapter on back pain in horses, a major problem in this species.

Returning to man, there are chapters on 2 pain models, 1 the measurement of late cerebral evoked potentials to painful cutaneous laser stimulation and the other on the value of a simple nociceptive flexion reflex. While in both models it can be shown that analgesic drugs influence the measured end-point, can it be

said that such single acute measures adequately represent the experience of chronic pain? The enthusiasts for such models should interpret their results cautiously.

The multidimensional scaling approach to pain rating is presented at length and again discussion of complex measurement theory is necessary. The psychometric 'global pain maps' produced by such measures contrast strikingly with the relatively simple neurophysiological measures of pain to be found elsewhere in this book.

There is no doubt that this is a special interest book, a source which should be consulted by anyone planning a clinical study of chronic pain. It does not provide much practical guidance but it does give important background discussion of the major controversies and pitfalls, and amply reveals the lack of unanimity amongst the experts.

JOHN SCADDING

Recent Achievements in Restorative Neurology. 3. Altered Sensation and Pain. Edited by Milan R. Dimitrijevic, Patrick D. Wall and Ulf Lindblom. 1990. Pp. 214. Basel: Karger. Price £82.50.

This slim volume works out at about 40p a page — or would if every page were of equal value. As it turns out, the purchaser would be paying out about 80p for every page worth reading. Much of the rest is devoted to the boiling of pots — an activity in which we all indulge at symposia, but hope not to see the results published. It represents the proceedings of a symposium held 18 months ago, but in common with railways and airlines, the publishers offer no rebate for late arrival.

Ulf Lindblom gives an interesting classification of altered sensation, which he has amplified at more recent conferences. This reviewer at least (who was not present at the original symposium) has found this author's more recent verbal expositions clearer than his written one. Bob Boas (the thinking man's anaesthetist) shows how nerve blocks can be used to clarify the pathophysiology of pain. Beric offers a further exposition of the interesting classification of spinal cord injuries on which he and various colleagues have been working for several years. Borvie and Leijon write a preliminary account of their excellent work on central poststroke pain ('thalamic syndrome') which appeared in a fuller version in *Pain* towards the end of 1989. Sindou and Jeanmonod review neurosurgical procedures (including stimulation), mainly at the level of spinal roots and cord, for pain relief, but tell the reader that space does not permit them to list the 102 publications to which they refer. This reviewer cannot believe that the neurologically eminent editors of this symposium would forbid the printing of the bibliography to a *review*, of all things. So who can be guilty of this crass solecism, which in itself would justify demanding a 50% reduction in the price of the volume?

Ochoa's brief chapter on personal experience of neurological dysfunction is one of the jewels of this symposium. I wonder if, like the reviewer, he got intense paraesthesiae in the lower leg and foot (S1 in his case, L5 in mine) on orgasm following operative interference with the root? This phenomenon has also been reported by some patients not only with root disturbances, but also with central (poststroke) pathology, though of course in the latter case the distribution is not dermatomal.

Besson and his colleagues offer a novel explanation for the reduced (or absent) susceptibility to morphine which is such a marked feature of deafferentation pain, based on the reduction in morphine receptors when central primary afferent terminals are removed. This interesting hypothesis may hold some water in the case of actual physical deafferentation; but how could it be fitted to the physiologically similar pain with sensory deficit which may occur following central lesions? Willis adduces some interesting evidence in favour of a role of wide dynamic range neurons and the spinothalamic tract in hyperalgesia (or allodynia?). Since anterolateral cordotomy, destroying the upward projection of these cells, fails to relieve neurogenic pain, and pathological destruction of their relay in the ventrobasal thalamic nucleus may actually *cause* it, one wonders why so many authors cling to the spinothalamic tract as 'the pain pathway' in the teeth of all clinical evidence? For good measure, it may be pointed out (again) that removal of the postcentral gyrus, to which the ventrobasal thalamus projects, results in the loss of all somatic sensations *except* pain.

The symposium ends with thoughtful contributions by Marshall Devor and Patrick Wall. Neither offer solutions, but they certainly make the reader think, as do some of the other authors mentioned. This is what the whole of a volume like this should do, but doesn't.

DAVID BOWSHER

Clinical Neurophysiology of the Vestibular System. Edition 2. By Robert W. Baloh and Vincente Honrubia. Contemporary Neurology Series. 1990. Pp. 301. Philadelphia: F.A. Davis. Price £38.79.

The authors' avowed intention stated in the preface to this volume is 'to provide a framework for understanding the pathophysiology of diseases involving the vestibular system'; in this, they have succeeded admirably and, moreover, have provided a disciplined *modus operandi* for the clinical investigation and management of the dizzy patient.

The text opens with an introductory account of the anatomy and physiology of the peripheral and central vestibular systems. This is followed by a guide to the clinical evaluation of the dizzy patient including case histories illustrating different causes and types of 'dizziness' and an extensive account of neurophysiological testing procedures, including relevant audiological investigations. Here the vestibular scientist may find cause for reflection for, whereas audiometric tests have documented high rates of success in identifying pathology and distinguishing the normal from the abnormal, it is not clear that the newer (and expensive!) vestibular investigations, such as rotational testing, have such power and are worthy of the financial investment required to set them up in a clinic. The authors illustrate the kind of results one can obtain from the various vestibular tests and one should note, in particular, that the test data have high variance which implies poor specificity and sensitivity. This useful section should, therefore, be read with care by any clinician who is wondering about which tests to add to his battery. A final substantial portion of the book is an account of the major peripheral and central disorders affecting the vestibular system and a critical evaluation of their pharmacological and surgical management.

The overall hierarchical organization of the text and quality of design and illustration are excellent. Effective use of subheadings is made so that one can find subjects of interest with ease. Individual topics are dealt with in separate, clearly headed sections which are concise and relevant. Each section provides introductory explanations of the topic which will be clear to the student, gives a useful summary of established facts, and also frequently takes the reader to the frontier of current knowledge and research.

The text has shortcomings. The sections concerned with the physiology of vestibular spinal and collic control are brief considering the body of recent literature, concerned with studies of vestibulospinal interaction, which is relevant to understanding ataxia of vestibular origin. The corresponding discussion of patients' symptoms and signs is largely concerned with vertigo and eye movements to the neglect of disabilities such as ataxia, veering and loss of spatial orientation in darkness. There is also a paucity of information on psychological and rehabilitative approaches to the dizzy patient which is surprising since an enduring problem for the neuro-otologist is that of managing patients who do not adjust well to vestibular imbalance.

In conclusion, one should emphasize how easy it is to read this book by reason of good design and a beautifully clear writing style, which undoubtedly reflects the authors' mastery of their subject. The volume deserves a place, not only in the medical library and otological laboratory, but also on the desk of any clinician concerned with managing the dizzy patient.

MICHAEL GRESTY

Neuroendocrine Perspectives, Volume 7. Edited by E.E. Müller and R.M. McLeod. 1989. Pp. 178. Heidelberg: Springer. Price DM 138.00.

Volume 7 of the *Neuroendocrine Perspectives* series includes some very exciting and thoughtful papers. For me, the most novel was the masterly review of the state of knowledge with regard to neuronal cell growth, maintenance and potential for regeneration by Drs Skaper, Leon and Toffano. We are provided with a panoramic view of growth factors and growth factor modulating agents, cell culture, bio-assay systems, the current use of chemically defined culture systems and insight into the molecular mechanisms of growth factor-mediated events. In addition, they review current evidence with regard to *in vivo* involvement of neuronotropic and neurite-promoting factors as well as suggestions of pathogenetic results of the absence of such trophic factors and their possible therapeutic potential.

Millington and Cronwell provide a very clear view of the dopaminergic regulation of the intermediate pituitary. This has served to elucidate interesting interactions between ion channels and secretory activity.



receptor binding and stimulation of second messenger systems, as well as elucidation of subsequent influences on transcription and posttranslational processing.

The NIH group of Dr Chrousos and colleagues provides a well reviewed overview of corticotrophin releasing hormone, its pharmacology and pharmacokinetics and their experience with this peptide in the pathophysiology of hypothalamic-pituitary-adrenal disorders. The area of the review discussing the inter-relationship of this system with clinical depression illustrates well the difficulties of relating endocrine/pharmacological parameters to our knowledge of this complex disease process.

Finally, Phyllis Wise provides a marathon review taking into account 437 references to analyse the ageing of the reproductive axis in terms of changes in the length and variability of reproductive cycles, changes in ovarian function and changes in neuroendocrine function. Account is made of data both in man and laboratory animals, attempting to dissect out at every level changes related to ageing and their independence or interdependence with other factors. Although there was little consideration for a potential role of inhibin(s), the review was basically as complete as any such chapter could be.

In conclusion, this volume of *Neuroendocrine Perspectives* provides some very well written and thought-provoking reviews which will certainly make a useful addition to my library shelf.

STAFFORD LIGHTMAN

Parallel Distributed Processing. Implications for Psychology and Neurobiology. Edited by R.G.M. Morris. 1989. Pp. 339. Oxford: Clarendon Press. Price £40.00.

Over the last 10 years there has been a renewed interest in the implications for computer science and neurobiology of the architecture of the central nervous system, parallel distributed networks and neural modelling. As pointed out in the preface to this report of a one day meeting held in Oxford in 1988, this period coincided with development of attempts to determine how complex networks of neurons might perform the various tasks that underlie perception, cognition and behaviour. The book attempts to integrate the varying areas of investigation that are essential for these tasks.

Whilst being essentially a proceedings publication, this volume achieves considerably more in that it provides a useful review of a wide area of investigation, not simply the immediate areas of interest of the speakers. The initial chapters deal specifically with the basic mathematical and computing models that are the essential basis of the neural network approach. They are accessible, however, only to those with a level of initial knowledge and for a general scientific and medical audience a more didactic approach would have been valuable. The second section deals with the implications of these connectionist models for psychology. These chapters are both interesting and informative and indicate the potential for the application of 'top-down' approaches in determining the neural basis of psychology. This section is clearly introduced and positive aspects of parallel distributed processing (PDP) are highlighted in the subsequent chapters. It is worth noting that whilst PDP models 'can serve as the source of new theoretical, and perhaps even empirical, insights. . . . this is not unique', to quote Humphreys' succinct introduction to this section. Alternative approaches are indicated but not emphasized.

As a neurobiologist I was drawn most readily to the final section which has a useful, if brief, introduction by the editor. This introduces successfully the 'bottom-up' approach to PDP modelling — a reliance on the real anatomy and physiology as the basis of computational modelling. This form of analysis may have some similarities to basic PDP modelling but some essential differences remain. These are identified to a degree in the following chapters. Morris's formal presentation is an interesting fusion of 'top-down' and 'bottom-up'! Simple invertebrate nervous systems have often been believed to offer the ideal natural model for investigating basic processes of learning. Hawkins provides a detailed picture of the establishment of classical conditioned reflexes based on a computational model that has been developed from basic observations in *Aplysia* made with Kandel. In many ways his conclusions are the most important as they stress the inherent value of the individual neurobiological and computational approaches and the particular virtue of cross-fertilization between these modes of investigation. His belief that 'Although nervous systems have constraints which appear to be (and may actually be) restrictive, using biology as a guide in this manner may none the less turn out to be the best way to create computer models with some of the capabilities of real nervous systems' is supported by the subsequent chapters that provide insights into studies on synaptic plasticity and learning, the role of the hippocampus in information processing, and learning in the olfactory

cortex. The connectionist approach married to electrophysiology is shown to provide a powerful tool in determining the potential computational role of areas of the cortex. These investigations indicate the direction that will be taken in the future to understand the role of areas of the CNS in perception, learning and memory.

Overall, this is a most useful volume that has been compiled with thought and is much more than the usual compilation of papers presented at a meeting. It will have an audience in the three camps — computational scientists, psychologists and neurobiologists — but it will probably be read only by those already committed to the general approach reviewed. This is a pity, since there is a need for a book to encourage interest amongst final year honours students, intercalated BSc students and graduate students, including neurologists in training, in this expanding area of investigation of brain function. This will require a more didactic approach than that provided in this text. For the more experienced neuroscientist, neurologist or psychologist who persists, this is a challenging yet valuable book and one that should be available in a neuroscience section of a university library.

K.M. SPYER

Lesions Analysis in Neuropsychology. By Hanna Damasio and Antonio R. Damasio. 1989. Pp. 227. New York and Oxford: Oxford University Press. Price £34 00.

This book marks a significant advance at the interface of behavioural neurology and neuropsychological research. The Damasios, while inheriting the classical tradition of behavioural neurology in an unbroken (but not densely populated) line from Hughlings Jackson to Norman Geschwind, have set their own particular seal upon this discipline: the collation of fine-grain behavioural data with meticulous neuroanatomy.

Studies of brain-behaviour relationships, at the anatomical level, have been hampered in the past by the relative crudity of early techniques of neuroimaging. Thus in research on hemisphere asymmetry of function, for example, early claims to secure groups with unilateral lesions, on the basis of a CT scan, have now to be regarded with caution. Likewise, medicolegal reports suggesting that a negative CT scan eliminates brain injury are now outmoded by MRI scans, as a comparison of the two techniques in studies of closed head injury has convincingly demonstrated. The Damasios have exploited, to the full, contemporary advances in imaging techniques in order to give a more precise account than was hitherto possible of the neural substrate of behavioural deficits. Thus one of the substantial contributions of the book consists of 'road maps' to neuroanatomy with detailed technical prescriptions for neuroradiological and neuroanatomical analysis. Here is clinical and technical expertise of rare excellence that, in conjunction with closely observed behavioural data, beautifully illustrates the modularity — morphological and functional — of brain organization.

In discussing the 'lesion method' in humans, they explicitly repudiate an inappropriate attempt to localize function as such. And they concede that the lesion method relies on inferences based on the disruption of function rather than a direct study of 'normal' processing. But is this a true limitation? It could be argued that the experimental study of dyslexia and prosopagnosia in patients has contributed as much if not more to theoretical models of word and face processing than cognitive theory based on 'normal' performance. Certainly, data from the Damasios' laboratory have vindicated the lesion method, most eloquently perhaps in their studies of achromatopsia and prosopagnosia. Here, behavioural and anatomical observations in man begin to converge with rapidly increasing neurophysiological knowledge of the multichannelling of visual information in the primate brain.

One of the most original and much-needed achievements of this laboratory is to fractionate the so-called 'frontal syndrome' into its dissociable components — cognitive, social, and emotional. In particular, they have focused on a notorious gap in our understanding of the anatomical basis of the inappropriate behaviour and sociopathy that can occur in patients with well-preserved cognitive ability and even superior performance on familiar, well-standardized intelligence tests: a contrast that has been familiar, to clinicians, at an anecdotal level, since the accident a century ago of Phineas Gage whose frontal lesion, due to an errant crowbar, produced a marked personality change in the absence of obvious intellectual deficits.

A central feature of the book is its 'neural organization model', which encompasses many of the features, implicit or explicit, in current cognitive theory, including parallel and distributed processing, and neuron group selection. It differs from these in that it explicitly envisages convergence zones (in more rostral, higher association cortices, the limbic system, the thalamus and the basal ganglia) with binding codes which

instantiate the temporal and spatial coincidences of memory and which serve to reactivate the representations of memory by retroactive feedback.

Thus according to this view, memories are not laid down as 'engrams' in the circuitry but have to be reconstructed by the coactivation of upstream cortical regions where visual information is processed in a retinotopic coordinate system. This concept appears to lend itself to experimental exploration, and has already received some support from neurophysiological research. Singer recently reported that separate regions in the visual cortex of the cat were activated synchronously, in association with the perception of a specific object. The central device needed to trigger that activity must have some of the properties of Damasio's 'convergence zones' which drive the retroactive activity and thus re-evolve mental representations in the relevant association cortices of the modalities concerned.

The theory embodies a complex system of processing, capable of multiple modes of operation: 'parallel, convergent, and divergent, nonlinear, recursive, and iterative'. Critics will point out that the bets are well-hedged. But they have the unenviable task of generating a more plausible alternative to account for the extraordinary richness and diversity of pathophysiological evidence. If, as Jacob suggested, evolutionary progress depends on a 'bricolage génial', then we must expect patterns of brain organization that do not lend themselves to a simple linear analysis.

This book, which is lucid and beautifully illustrated, will be invaluable for all neuroscientists interested in brain-behaviour relationships.

FREDA NEWCOMBE

Linguistic Investigations of Aphasia. Second Edition. By Ruth Lesser. 1989. Pp. 234. London: Cole and Whurr. Price £17.50.

There are two reasons why this second edition of Ruth Lesser's *Linguistic Investigations of Aphasia* is a most welcome addition to the literature in speech pathology. The first one relates to the need for linguistic investigations. This is emphatically spelt out by the following quotation by Roman Jakobson: 'Aphasia is first and foremost a disintegration of language and as linguists deal with language it is linguists who tell us what the nature of these disintegrations is.' The second reason is that, as the author sadly but quite rightly remarks, whilst the linguistic ideas introduced into aphasiology over the last couple of decades have now become germane to the study of aphasia 'they have penetrated less well into the medical world' and 'into routine clinical practice'. An up-to-date and comprehensive survey of linguistic approaches, one which is accessible to clinical practitioners, may help change this situation.

The book is organized into 9 chapters. The first 3 chapters follow the principles of the first edition in that they provide an outline of medical and clinical descriptions of aphasia on the one hand, and an account of those linguistic concepts which are relevant to aphasia on the other. Chapter 4 deals with higher-order cortical dysfunctions commonly found in aphasia which might bear directly on an accompanying language dysfunction. There is an interesting and up-to-date discussion on the dichotomy of automatic and voluntary processing.

Chapters 5–9 constitute the actual survey of linguistic investigations of aphasia. Language processing, like other mental processes, is organized into discrete but cooperating modules, corresponding to the three main subsystems of language, namely the semantic, syntactic and phonological subsystems. Investigations into the impairment of each of these subsystems are reviewed. The chapters on semantic investigations gives a comprehensive account of the studies relating to semantic representations, lexical retrieval and factors affecting it. The very important point is made that more studies are needed which examine patients' abilities to use words in sentential context rather than in isolation. The discussion on syntactic impairments provides some useful methodological information regarding data collection. The question of disassociation between speech production and comprehension in relation to agrammatism and paragrammatism is discussed in detail. The chapter on phonological impairments is extensive and details three prevalent approaches: those which focus on neuromuscular disorder, those which focus on regular linguistic patterns in encoding and those which regard phonological disorder as a central disorder. The last chapter explores the latest linguistic theoretical concepts in terms of Joan Bresnan's Lexical Functional Grammar and Noam Chomsky's Government and Binding Theory and their application in cognitive neuropsycholinguistics.

This chapter also deals with sociolinguistic applications, in particular with so called 'functional communication' and investigations of language above the sentence level.

Appropriately for a survey of this kind the scope of the book is vast and it contains a wealth of information as well as a most extensive bibliography. A great majority of the studies described have taken place in the USA. It would have been nice to see some of the work currently being carried out in the UK also included. For anyone new to the field this is an excellent and stimulating introduction, but for those who have read the first edition it may be somewhat disappointing. It is a pity that most of what constitutes the major new advance, namely the application of cognitive neurolinguistics and pragmatics, has been compressed into 17 pages in a single chapter at the very end of the book. For the rest it is very much like the first edition. There are a few unfortunate oversights as far as updating is concerned. Many developments which were accurately described as 'recent' in the first edition 11 years ago must surely have lost some of their novelty value by now, but are still described as such. A more rigorous updating of the referencing is required. For example Roman Jakobson's quotation cited above appears on p.23 as 'in press'. It was already 'in press' 11 years ago. One wonders who the publishers were!

KLARA DORMANDY

ANNOUNCEMENTS

Clinical Autonomic Research Society

The Annual Meeting of this Society will be held at St Mary's Hospital Medical School, London, on November 16, 1990. Further information may be obtained from Dr David Jordan, Department of Physiology, Royal Free Hospital Medical School, Rowland Hill Street, London NW3 2PF, telephone (071) 794-0500, extension 4304.

Recent Developments in Child and Adolescent Psychiatry

This course will be held on December 6 and 7, 1990, at the Institute of Psychiatry, London, organized jointly by the Institutes of Psychiatry and Child Health, University of London. For information, contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF.

Ninth International Congress of Electromyography and Clinical Neurophysiology

This will be held in Jerusalem, Israel, on June 2-6, 1991. Further information may be obtained from Dr A. N. Gilai, PO Box 29334, Tel Aviv 61292, Israel.

Fifteenth International Symposium on Cerebral Blood Flow and Metabolism

This will be held at the University of Miami (James L. Knight International Center, Miami, Florida, USA) on June 1-6, 1991. Further information may be obtained from Jenny Bernal, School of Continuing Studies Office of Conferences and Institutes, University of Miami, PO Box 248005, Coral Gables, Florida 33124-1610, USA.

Fifth Annual Magnetic Resonance Imaging Conference

Organized by the Barrow Neurological Institute of St Joseph's Hospital and Medical Centre, this conference will be held on March 16-20, 1991. Further information may be obtained from Kevin King, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA.

Barrow Neurological Institute Eighteenth Annual Symposium

This symposium, which will be held at Marriott's Camelback Inn Resort, Scottsdale, Arizona, on March 21-23, 1991, will be devoted to 'Recent Advances in Neurology and Neurosurgery'. For further information, contact Tony A. Jardine, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA.

International Quincke Symposium

This symposium, organized under the auspices of the World Federation of Neurology, will be devoted to Barrier Concepts and Cerebrospinal Fluid Analysis. It will be held in Göttingen, on September 19–21, 1991. For information, contact Professor K. Felgenhauer, Neurologische Universitätsklinik, Robert-Koch-Strasse 40, D-3400 Göttingen, FRG.

British Aphasiology Society

A conference will be held at Sheffield University on September 19–21, 1991. Abstracts of papers not exceeding 150 words with an accompanying summary of not more than 500 words (2 copies of each) should be sent, by March 31, 1991, to Dr Graham Venables, Department of Neurology, The Royal Hallamshire Hospital, Sheffield S10 2TN.

American Association of Electrodiagnostic Medicine

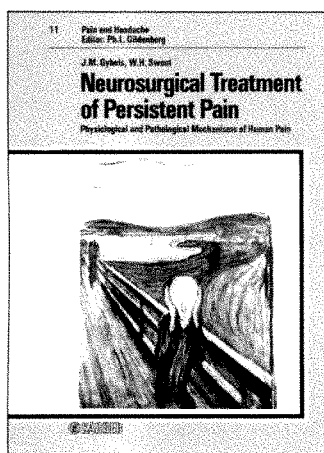
The AAEM will be sponsoring four 'hands-on' regional workshops in the Spring of 1991 at Denver (February 22–24), Chicago (March 9–10 and 15–16) and Washington, DC (March 23–24). For details and registration form, contact the AAEM, 21 Second Street SW, Suite 306, Rochester, MN 55902, USA.

Medical College of Wisconsin

A course on 'Imaging the head, spine and musculoskeletal system: a discussion of protocols and applications' will be held at the Westin Kauai Resort in Kauai, Hawaii on February 17–22, 1991. For details, contact Marti Carter, CME Inc., 11011 West North Avenue, Milwaukee, WI 53226, USA.

Third International Workshop on the At Risk Infant

This will be entitled 'The developmental neurobiological basis for early intervention: animal models and human data—guidelines for practice', and will be held in Jerusalem on July 1–5, 1991. For further information, contact The Third International Workshop on the At Risk Infant, c/o International Ltd, PO Box 29313, 61292 Tel Aviv, Israel.



Gybels, J.M. (Leuven); Sweet, W.H. (Boston, Mass.)
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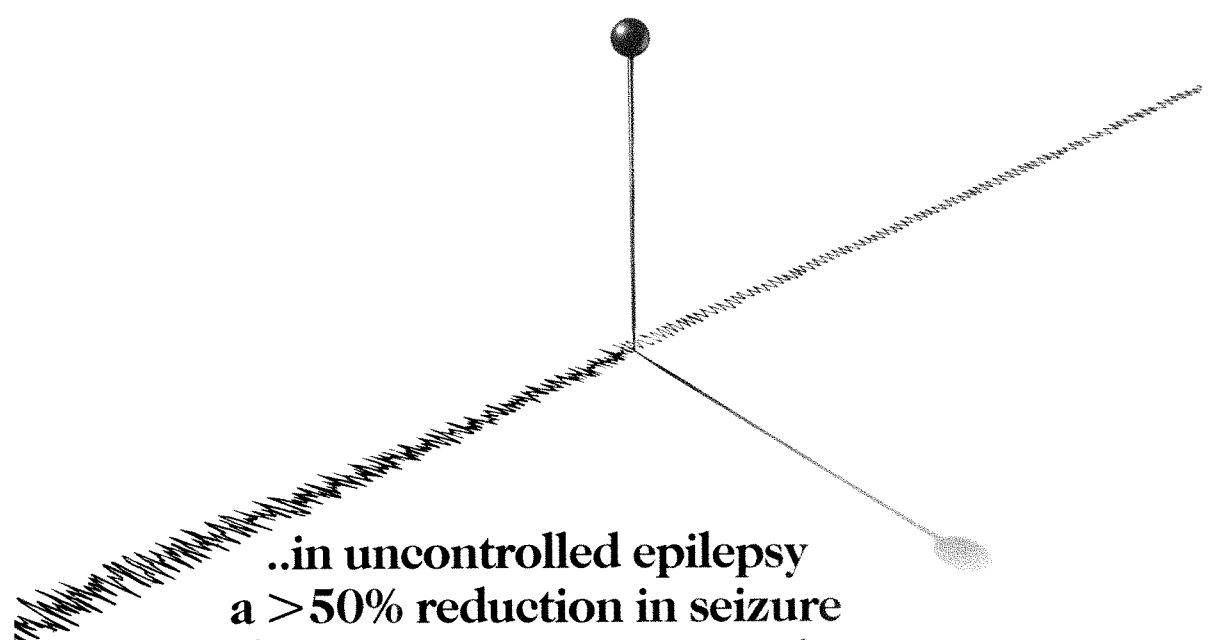
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Continued on inside back cover

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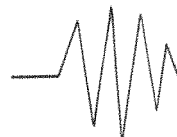
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Presentation White, oval biconvex tablets with a breakline on one side and SABRIL on the other. Each tablet contains 500mg vigabatrin. **Uses** *Mode of Action* A selective, irreversible inhibitor of GABA-transaminase. Treatment leads to an increase in brain levels of GABA (gamma-aminobutyric acid). **Indications** Indicated for the treatment of epilepsy which is not satisfactorily controlled by other antiepileptic drugs. **Dosage and Administration** For oral administration once or twice daily and may be taken before or after meals. **Adults** The recommended daily starting dose is 2g (4 tablets) which should be added to the patient's current therapeutic regimen. The dose may be increased or decreased in 0.5g or 1.0g increments depending upon clinical response and tolerability. Increasing the dose above 4g/day does not usually result in improved efficacy. There is no direct correlation between plasma concentration and efficacy. The duration of the effects of the drug are dependent on the rate of enzyme re-synthesis rather than the concentration of drug in the plasma. **Children** The recommended daily starting dose is 1g (2 tablets) in children aged 3-9 years and 2g (4 tablets) in older children. **Elderly** Doseage reduction may be necessary in patients with impaired renal function, particularly patients with creatinine clearance less than 60 ml/min. See "Precautions." **Contra-indications** Contra-indications, **Precautions**, **Warnings** etc. **Use in pregnancy and lactation** Use of Sabril during pregnancy is contra-indicated. There is no evidence of the safety of Sabril treatment whilst breast-feeding and so it is not recommended. **Precautions** As with other antiepileptic drugs abrupt withdrawal may lead to rebound seizures. If treatment is to be discontinued it is recommended that this is done by gradually reducing the dose over 2-4 weeks. Sabril should be used with caution in patients with a history of psychosis or behavioural problems (see under side-effects). Caution should be exercised when administering the product to elderly patients and more particularly patients with creatinine clearance of less than 60 ml/min. Reduced doses should be used and patients monitored closely for adverse events such as sedation and confusion. **Warnings** Animal safety studies indicate that vigabatrin causes intramyelino oedema in the brain white matter tracts. Currently there is no evidence to suggest that this effect occurs in man. However, it is recommended that patients treated with Sabril are closely observed for adverse effects on neurological function. Details of animal findings are given under "Further Information" in the full product data sheet. **Effects on driving ability** Drowsiness has been observed and patients should be warned of this possibility before treatment. 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CLINICAL ASPECTS OF MULTIPLE SCLEROSIS IN NORTH-EAST SCOTLAND WITH PARTICULAR REFERENCE TO ITS COURSE AND PROGNOSIS

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SUMMARY

The prognosis and course of multiple sclerosis (MS) and the factors that affect them were assessed in a group of 1055 patients, representing an unselected (epidemiological) sample observed in the north-east (Grampian region) of Scotland for a period ranging between 1 and 60 yrs. In 7% the disease began before the age of 20 yrs, in 12% after the age of 50 yrs, and in the remainder onset was between the ages of 20 and 50 yrs. The male/female ratio was 1:1.8. Mean disease duration in those observed until death (216 patients) was 24.5 yrs, with no significant difference between the sexes. Prognosis was assessed either by the interval between onset and death or by the degree of disability over a defined period of time. Depending on the length of follow-up, just over one-quarter (26%) to over one-third (36.3%) had a benign course and between 8.0 and 17.7% had a poor prognosis. Nearly a third had a remittent (32.8%) or relapsing cumulative (34%) course and 9% had a progressive course from the start. Several factors were noted to affect the prognosis.

Prognosis was significantly better, independent of sex, in those with (1) an early onset (<40 yrs of age); (2) retrobulbar neuritis or a brainstem lesion or sensory symptoms alone at onset; (3) short duration of initial symptoms (<6 months); (4) a long onset–first relapse interval (>1 yr); (5) a remittent course in the beginning and (6) lack of a family history of MS. The factors which predicted a poor prognosis included: (1) a late onset (>40 yrs of age); (2) progressive course from the start; (3) multiple sites of lesions initially, or a cerebellar or spinal cord lesion at the onset; (4) psychiatric or persistent urinary symptoms at the onset or within 10 yrs; (5) persistent initial symptoms (beyond 1 yr); (6) early first relapse (within 6 months); (7) a family history of MS; (8) social class status IV and V; and (9) bilaterally prolonged visual evoked potential (VEP) P100 latency. Address in childhood and at the onset of the disease, changes in the CSF and CT brain scan were not of predictive value.

INTRODUCTION

There have been only a few studies analysing the prognosis and course of multiple sclerosis (MS) in patients observed for a long period and derived from a prevalence source (Allison, 1950; Hyllested, 1956; Gruber, 1962; Panelius, 1969; Gudmundsson, 1971; Percy *et al.*, 1971; Leibowitz and Alter, 1973; Broman *et al.*, 1981; Clark *et al.*, 1982; Poser *et al.*, 1982a) and only one of these (Broman *et al.*, 1981) was based on a prospective analysis. Studies based on a selected group of MS patients observed in a hospital have been many (Millar, 1949; Müller, 1949; Carter *et al.*, 1950; Ipsen, 1950; Lazarte, 1950; MacLean and Berkson, 1951; McAlpine and Compston, 1952;

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Thygesen, 1953; Abb and Schaltenbrand, 1956; McAlpine, 1961, 1964; Lehoczky *et al.*, 1963; Poeck and Markus, 1964; Bauer *et al.*, 1965; Bonduelle, 1967; Fog and Linnemann, 1970; Riser *et al.*, 1971; Kurtzke *et al.*, 1977; Confavreux *et al.*, 1980; Noseworthy *et al.*, 1983; Verjans *et al.*, 1983; Thompson *et al.*, 1986), the majority of these have been retrospective and often biased towards patients at the severe end of the disease spectrum.

The US male war veterans study (Kurtzke *et al.*, 1977), although not on a prevalence sample, did encompass a clearly defined population and with some reservations could be considered as representative of the disease in that group. Müller (1949) analysed a fairly large representative sample of patients attending hospital in Stockholm but diagnostic facilities during the period of the study were not well developed and it is likely that a proportion of his cases may not have had MS. McAlpine and Compston's (1952) and McAlpine's (1961, 1964) often quoted classical study did represent a large sample but it was probably on a selected group of patients attending hospital biased towards the severe end of the disease spectrum, as suggested by the short mean survival period of 11 yrs.

The north-east of Scotland has been under close epidemiological scrutiny for MS since 1970. Three major surveys have been carried out in the region between 1970 and 1981 (Shepherd and Downie, 1978, 1980; Phadke and Downie, 1987). In 1970, besides analysing the incidence and prevalence of MS, a register was also established. The clinical and laboratory information for all patients seen subsequently was recorded on index cards and periodically updated. Mortality data were collected periodically and have been reported elsewhere (Phadke, 1987).

Some of the clinical features of the disease noted in the 1970 survey have been documented previously (Shepherd, 1979). On the basis of the information collected during the latest survey (Phadke, 1985) a further analysis of the clinical features was undertaken. Data have been generated about the natural history of the disease which should prove helpful in counselling MS patients.

Very few authors have attempted to compare the different clinical features, in particular, the course and prognosis of MS in different parts of the world (Poser, 1978; Shibasaki *et al.*, 1981; Kuroiwa and Kurland, 1982). Many difficulties exist in carrying out such a comparison. These include differences in diagnostic criteria, analysis of a selected sample with its inherent drawbacks—often from an inpatient source only, and frequently biased towards the severe end of the disease spectrum, or with a small sample size often followed for a short period and often analysed retrospectively; and, finally, lack of uniformity in the definitions of various clinical parameters such as course, prognosis, relapse, etc.

It has been observed that MS in eastern centres such as Japan (Kuroiwa *et al.*, 1975), Taiwan (Hung *et al.*, 1976), China (Baoxun *et al.*, 1982) and India (Mathew *et al.*, 1971), presents differently with a much higher frequency of early, severe, and often bilateral optic neuritis and with a male preponderance. Comparison of certain clinical aspects of the disease amongst western centres has been attempted twice (Poser, 1978; Shibasaki *et al.*, 1981) but precise conclusions could not be reached. A further comparison, including findings of the present sample, has been undertaken in the latter half of this paper.

MATERIAL AND METHODS

Details of the incidence and prevalence of MS in the region have been published elsewhere (Shepherd and Downie, 1978, 1980, Phadke and Downie, 1987). During the final survey (Phadke and Downie, 1987), other than the demographic data, a number of clinical and laboratory details were stored on a mainframe computer. Data were recorded initially on index cards for all individuals known at the 1970 survey and subsequently until 1981. Information on these cards was regularly updated on the basis of letters from the hospital visits, from the case notes, VEP register, personal examination of all chronically hospitalized patients and from the questionnaire answered by all the general practitioners of the region during the three postal surveys. The last of the above sources provided information regarding the current state of disability and the number of relapses since the last hospital visit.

The questionnaires were on a standard proforma which contained, amongst other things, an abbreviated form of the McAlpine's disability scale as a guide line. Based on the total available information, patients were classified using modified criteria of Allison and Millar (1954). The two subdivisions of the probable category of these criteria were merged into one for convenience; thus '*probable*' MS included patients with a history and physical signs of CNS disease, disseminated in time and site of involvement, in whom other neurological conditions had been excluded so far as possible. Also included in this category were patients seen at an earlier stage of the disease with a clear history of remission and relapses but with few physical signs of a CNS lesion, and in whom the clinical diagnosis of MS was supported by laboratory evidence such as a raised percentage concentration of IgG in the CSF, prolonged VEP P100 latency or a periventricular low density area on CT scan of the brain. The criteria for the '*possible*' category were similar to those given by Allison and Millar; thus the '*possible*' category included those with clinical findings compatible with MS in whom other diagnoses had been excluded so far as possible; in some of these, evidence of multiplicity of lesions was, however, lacking. This category also included some patients with a late onset progressive spastic paraparesis in whom full investigations, including myelography, had excluded other likely causes of such a clinical picture.

The above categorization of the patients was carried out in joint consultation with Dr A. W. Downie, who had been closely involved in the local MS project since its inception. Patients with isolated optic neuritis and those with diagnostic uncertainty on clinical grounds were excluded. The degree of disability amongst those living at the time of the latest survey (1981) was combined with the duration of the disease to form 7 prognostic categories, McAlpine and Compston's (1952) disability grading was used. Those who died between the years 1970 and 1981 were grouped under a separate—eighth—category. The classification of Confavreux *et al* (1980) was used as a basis for the following 8 prognostic groups.

1. *Benign*. Patients with the least severity, who had no disability at 10 or more yrs after the onset of MS, or who had grade II disability at 15 yrs and above.
2. *Moderate*. Patients with a disability of grade III and above and a disease duration exceeding 30 yrs.
3. *Intermediate*. Patients with a disability of grade III and above and a disease duration ranging between 21 and 30 yrs.
4. *Subacute*. Patients with a disability of grade III and above and a disease duration ranging between 11 and 20 yrs.
5. *Acute*. Patients with a disability of grade III and above and a disease duration ranging between 6 and 10 yrs.
6. *Hyperacute*. Patients at the most severe end of the disease spectrum, who had disability of grade III and above within 5 yrs of the onset of the disease.
7. *Unclassified*. Patients with either no disability but with a relatively short disease duration under 10 yrs, or a minimal disability (grade II) at 15 yrs from the onset.
8. *Dead*. All deaths from the patients identified in the first survey (1970), and also those diagnosed until the third survey (1981), numbering 216 patients. The clinical details of this group including the influence of various factors on the period of survival have been published elsewhere (Phadke, 1987).

In addition to analysing the prognosis of the 1055 patients identified in the 1970 and/or 1981 surveys in the above manner, an unselected group of 672 patients observed for over 10 yrs was evaluated separately. This subgroup represented an unselected (prevalence) sample of those patients who lived in the region at the 1970 survey and whose prognosis in terms of the extent of morbidity or mortality until 1981 was known. The purpose of this separate analysis was to assess the prognostic value of the degree of disability

at a point in time for an unselected cohort of patients observed for a reasonably long period in excess of 10 yrs.

The course of the disease from the onset to the point of the latest survey was analysed separately for the total 1055 patients, based on the classifications of Confavreux *et al.* (1980) and Poser *et al.* (1982b). The following four categories were made.

1. *Remittent*. Those in whom the disease was in complete remission without any resultant disability at the time of the latest survey, or until just before death amongst those observed until then.

2. *Relapsing cumulative*. Patients who had a stepwise increase in the disability following each relapse until the time of the latest survey, or just before death amongst those observed until then.

3. *Relapsing progressive*. Those in whom the initial disease pattern was remitting-relapsing in nature followed later by relentlessly progressive increase in disability until the time of the latest survey, or until death in those observed until then.

4. *Progressive*. Those in whom the disability inexorably increased without remission between onset to the point of the latest survey or until the time of death in those observed until then.

McAlpine's (McAlpine and Compston, 1952) definitions for onset of the disease, relapse and remission were adhered to.

The CSF IgG was estimated using agar gel electrophoresis and results were expressed as a percentage of the total protein in the CSF. VEPs were recorded using pattern reversal at 1/s averaging 128–256 sweeps for each eye separately. The following clinical and laboratory parameters were correlated with the prognosis and course using a mainframe computer to assess the predictive value of each of these parameters. (1) Age at onset; (2) sex; (3) address at onset of the disease and during childhood; (4) presence or absence of a family history of MS; (5) social class at the onset of MS; (6) occupation at onset; (7) pattern of initial symptoms; (8) whether the onset was monosymptomatic or polysymptomatic; (9) anatomical site of the initial CNS lesion diagnosed on clinical grounds; (10) duration of the initial symptoms; (11) interval between onset and the first relapse (O–R interval); (12) VEP P100 latency; (13) CSF findings including percentage IgG; and (14) changes on the CT brain scan.

The χ^2 test, or Mann-Whitney U test were used to assess the level of significance. Appropriate correction in *P* value was carried out in multiple group comparisons.

Comparison of the worldwide clinical pattern of MS

Publications prior to 1949 were excluded because of a relatively small number of patients or nonavailability of precise clinical information about patients in most instances. All cases were included in each study, irrespective of their diagnostic category. Studies satisfying the following criteria were included.

1. Those studies where precisely defined diagnostic criteria were adhered to.

2. Those in which the patients were identified during an epidemiological survey or where they represented an unselected series of MS patients attending hospital or where the author(s) showed convincingly that the sample, albeit small, was representative of the disease in that region of the world. This latter point particularly applied to reports from the eastern centres.

3. Those studies where a sizeable number of patients had been observed for a period in excess of 10 yrs or where the interval between two epidemiological surveys was sufficiently long.

Figures from certain studies had to be rearranged to allow comparison. The following clinical parameters were compared.

1. Age at onset—this was grouped into three: those under 20 yrs, those between 20 and 50 yrs and those over 50 yrs. Studies using Schumacher's diagnostic criteria (Schumacher *et al.*, 1965) were therefore excluded because of their imposed restrictions.

2. Sex distribution.

3. Frequency of various initial neurological symptoms. These were grouped under seven broad categories, viz, cerebral disturbance, e.g., seizures, hemiplegia with facial involvement, dysphasia, psychoses, etc.; retrobulbar neuritis; brainstem disturbances; cerebellar involvement; pyramidal involvement; sensory tract disturbances; and disturbances of micturition, e.g., precipitancy, incontinence or retention of urine.

4. Anatomical site(s) of initial lesion(s). The available information as to the initial localization was grouped under 8 anatomical sites as for the present sample.

5. Course of the disease. In only a few studies was such information available. Patients were grouped under the three categories, i.e., remittent-relapsing, relapsing-progressive and progressive, as defined

previously for the present sample. In certain studies patients were grouped into only two categories, i.e., relapsing-remitting and progressive; data from these were analysed separately.

6 *Prognosis of the disease.* This was judged by combining the degree of disability with the duration of the disease between onset to the year of the study or by the mean period of survival. To bring uniformity into the analysis of the degree of disability in various studies, comparison made by Detels *et al.* (1982) of the various commonly used disability grading systems was used as a guideline, after a few modifications.

The following five prognostic categories, different from those used for the present sample, were made because only limited information as to the degree of disability and duration was available in most published series.

1. *Benign.* Those with no or only minimal disability as in the classification of Detels *et al.* after 10 yrs from the onset.

2. *Intermediate.* Those with moderate to severe disability as in Detels' classification, after 10 yrs of the disease.

3. *Severe.* Those with moderate to severe disability as in the classification of Detels *et al.* within 10 yrs of onset.

4. *Unclassified.* Patients with no or only minimal disability as in the classification of Detels *et al.* within a relatively short observation period of under 10 yrs.

5. *Dead.* Those who died during the period covered by the study.

The χ^2 test was used to assess statistical differences in the various parameters between different centres. The Mann-Whitney U test was used for assessing the level of significance in multivariate analysis.

RESULTS

Present series

Duration of the disease amongst the 1055 patients known to exist between 1970 and 1980 ranged between 1 and 60 yrs. The male to female ratio was 1:1.8 (M = 372; F = 683).

Age at onset

Over three-quarters of the patients had an onset of the disease between the ages 20 and 50 yrs, 12% had an onset after the age of 50 yrs, and in 7% it was under the age of 20 yrs (fig. 1).

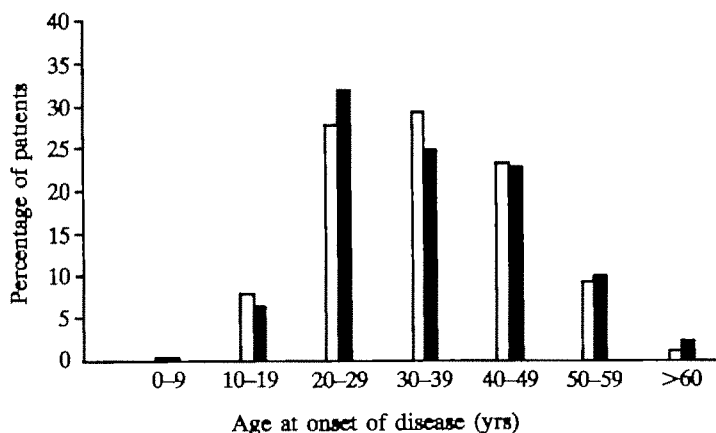


FIG. 1. Age at onset by sex (all patients observed between 1970 and 1980). Open squares = males (372), closed squares = females (683)

Prognostic categories

Out of the 1055 patients, just over a quarter had a benign prognosis. At the other end of the disease spectrum, only 8% fell into the hyperacute and acute prognostic categories; a fifth of the patients died during the period between 1970 and 1981, with a mean period of 24.5 yrs between onset and death. There was no statistically significant difference between males and females in the proportion of patients in the various prognostic categories, or in the period of survival. Just over a fifth were grouped under the unclassified prognostic category because of the relatively short period of observation (Table 1). This large number of patients observed for a short period naturally influenced significantly the overall proportion of patients in the other prognostic categories.

To overcome the drawback of a rather short observation period, the 1970 cohort (*see* Methods) was assessed separately. Analysis of these 672 patients (forming part of the total of 1055 patients) who were present in the region in 1970 and whose disease outcome after 10 yrs (in 1981) was known, is shown in Table 2.

Over one-third of the patients (36.9%) from this cohort had a benign prognosis (Category 1). Of those who were unrestricted in 1970 (McAlpine's disability grade 1) about three-quarters (71.8%) remained so in 1980. Just over a quarter (29.9%) of those with various other worse grades of disability in 1970 were dead by 1980. Of the 35 patients confined to bed, and of the 98 confined to a wheelchair in the year 1970, 85% and 68%, respectively, had died by 1980.

Course of the disease

Out of the 1055 patients in whom the disease course was known, in a third the disease had a remitting and relapsing cumulative pattern, in 9% it was progressive from the

TABLE 1 PROGNOSTIC CATEGORIES FOR MS

Prognostic categories		No. of patients	%
1. Benign	(disability grade I at 10 yrs+ or disability grade II at 15 yrs+)	274	26.0
2. Moderate	(disability grades III-VI + disease duration of 30+ yrs)	44	4.2
3. Intermediate	(disability grades III-VI + disease duration of 21-30 yrs)	90	8.5
4. Subacute	(disability grades III-VI + disease duration of 11-20 yrs)	114	10.8
5. Acute	(disability grades III-VI + disease duration of 5-10 yrs)	49	4.6
6. Hyperacute	(disability grades III-VI + disease duration <5 yrs)	36	3.4
7. Dead	(between 1970 and 1980)	216	20.5
8. Unclassified	(disability grade I + disease duration <10 yrs or disability grade II + disease duration <15 yrs)	232	22.0
Total		1055	100

McAlpine's disability grades (McAlpine and Compston, 1952) (abbreviated form)
 I = *unrestricted* but not necessarily asymptomatic; II = *partly restricted* but able to walk unaided; III = *markedly restricted*—walking with aids outdoors, IV = *housebound*—mobile at home only, with support, V = *wheelchair bound*; VI = *bed bound*—requiring total care.

TABLE 2 DISABILITY STATUS IN THE YEAR 1970 AND PROGNOSTIC CATEGORIES IN THE YEAR 1980

Prognostic categories in 1980	Disability status (McAlpine's grades) in the year 1970 (%)						Total*
	Unrestricted	Partially restricted	Markedly restricted	House-bound	Wheelchair-bound	Bedbound	
Benign	71.8	44.3	12.4	4.1	0	0	36.9 (248)
Moderate	0.4	3.2	13.3	10.2	13.3	5.7	6.0 (40)
Intermediate	5.7	14.6	22.8	22.4	11.2	5.7	12.5 (84)
Subacute	13.2	22.8	23.8	18.4	7.1	5.7	16.2 (109)
Acute	2.6	2.5	0	0	0	0	1.5 (10)
Dead	6.2	12.7	27.6	44.9	68.4	82.9	26.9 (181)
Total*	100 (227)	100 (158)	100 (105)	100 (49)	100 (98)	100 (35)	100 (672)

* Figures in parentheses are absolute numbers.

start, and in 22% the disease entered a progressive phase by the time of the latest survey in 1981, after an initially relapsing-remitting pattern (Table 3).

Prognosis and course and their relationship to various clinical and laboratory variables

When correlating various clinical and laboratory variables with the disease prognosis and course, the problem of lack of information on all aspects of the disease for every patient arose. As a result, with the exception of judging the influence of the age at onset on the course and the prognosis of the disease, and of the course on the prognosis in nearly the whole of the present sample, the influence of the remaining clinical and laboratory parameters was confined to those living in the region at the time of the latest survey in 1981. The numbers in whom correlation between various parameters was possible is shown as the denominator in figs 3-6 and Tables 4-8.

Prognosis and course of the disease by sex. No significant difference was noted between males and females, either in the pattern of the course or the prognosis of the disease.

Prognosis and course of the disease by age at onset. Prognosis could be correlated with the age at onset in 1039 patients (fig. 2): the younger the age, the better was the prognosis, both in terms of morbidity and the period of survival. Data regarding the latter aspect are published elsewhere (Phadke, 1987). Of those with onset under the age of 20 yrs, 43% had a benign prognosis compared with 12% of those over the age of 50 yrs; other age groups fell in between ($\chi^2 = 73.10$, $df = 4$, $P < 0.0001$). In

TABLE 3 COURSE OF THE DISEASE

Course categories	No.	%
1. Remittent	346	32.8
2. Relapsing-cumulative	359	34.0
3. Relapsing-progressive	232	22.0
4. Progressive	95	9.0
5. Uncertain	23	2.2
Total	1055	100

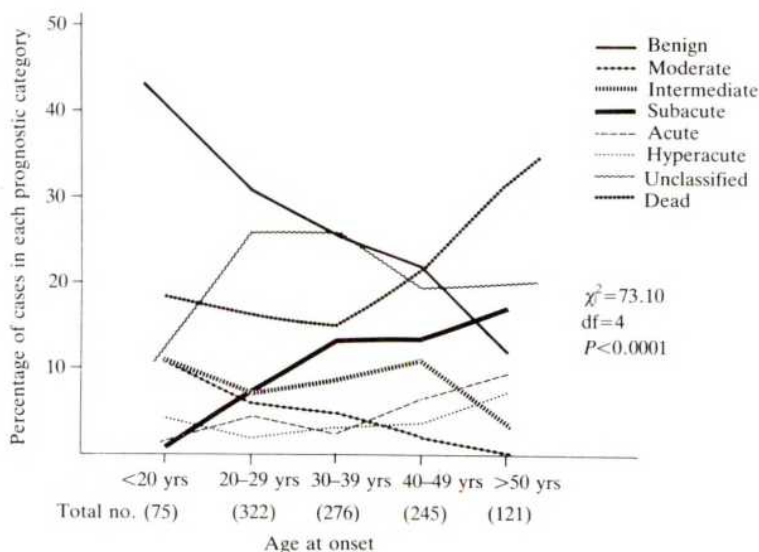


FIG. 2. Disease prognosis by age at onset.

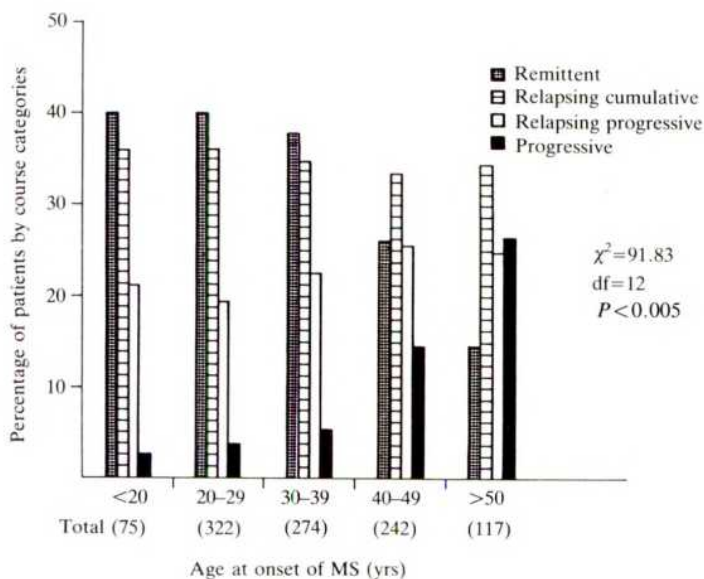


FIG. 3. Disease course by age at onset.

contrast to this, the proportion of patients with a severe prognosis (acute and hyperacute prognostic categories) rose from 5.3% in those with onset of the disease under the age of 20 yrs to 16.5% amongst those with onset over the age of 50 yrs.

The course of the disease could be correlated with the age at onset in 1030 patients

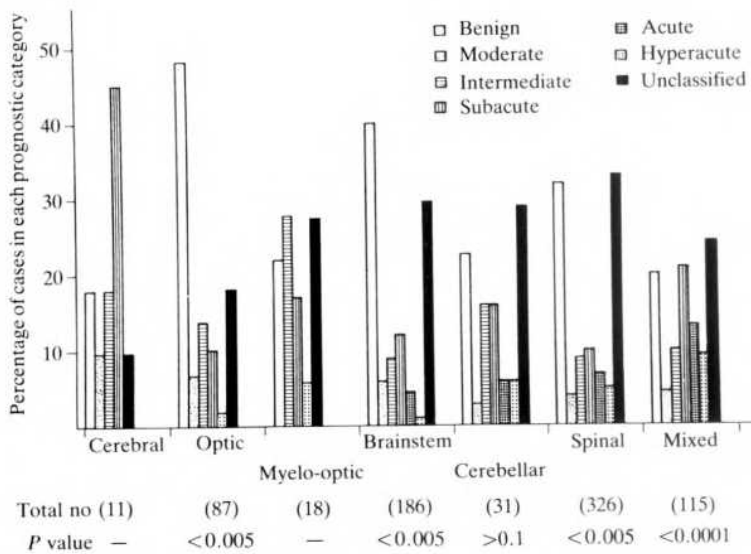


FIG. 4. Disease prognosis by initial site of CNS lesion.

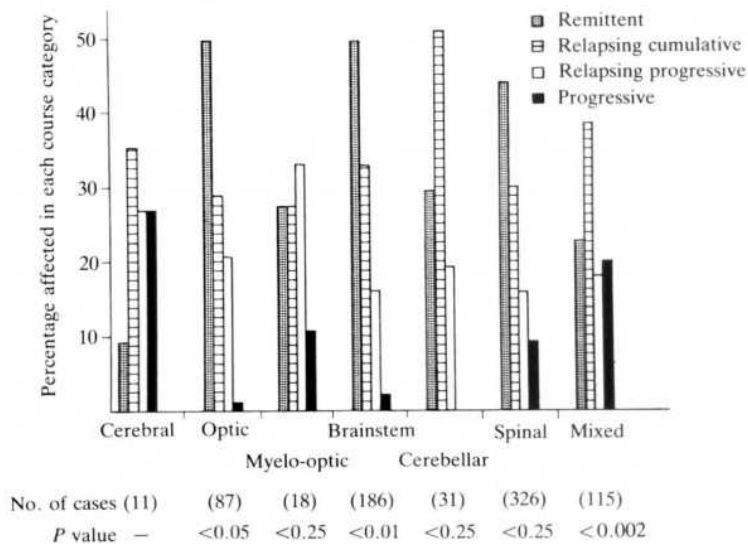


FIG. 5. Initial site of CNS lesion by course of the disease.

(fig. 3). The proportion of those with a progressive course either from the start or after an initially relapsing-remitting period progressively rose with age, 2.7% of those with onset under the age of 20 yrs had such a pattern compared with 26.5% of those with onset over the age of 50 yrs; the proportion of those with a remitting pattern of the disease correspondingly declined ($\chi^2 = 91.83$, $df = 12$, $P < 0.005$) (fig. 3).

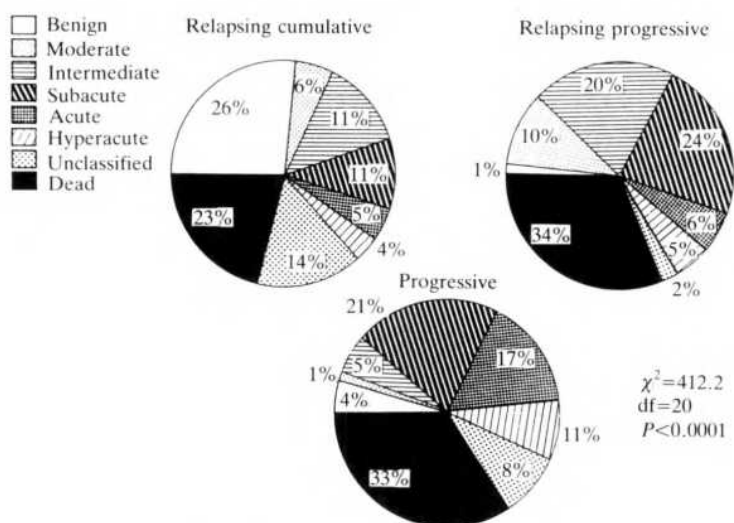


FIG. 6. Prognosis by course of the disease.

Prognosis by initial site of the lesion. The initial site of lesion was adjudged on the basis of the initial symptoms and examination findings in 774 patients. Those with an initial isolated optic neuritis or a brainstem lesion had a significantly better prognosis ($P < 0.005$) (fig. 4). In contrast, those with an initial spinal cord lesion or lesions at more than one site (mixed) had a significantly worse prognosis ($P < 0.005$) (fig. 4).

On analysis of the symptoms alone, those with initial gait ataxia (172 patients), usually due to cerebellar disturbance, or those with weakness due to a pyramidal lesion (436 patients), were noted to have a significantly worse prognosis (irrespective of sex) ($P < 0.002$). In addition, only amongst the females, an onset with symptoms of a cerebral lesion (25 patients) or of urinary disturbance (32 patients) also signified a worse prognosis ($P < 0.025$ and $P < 0.02$, respectively).

Males and females with symptoms due to a spinothalamic disturbance, and females alone with initial symptoms of posterior column disturbance, more often had a benign prognosis, although none of these groups achieved a statistical level of significance.

Course by the initial site of lesion. This could be correlated in 773 patients. Those with initial optic neuritis, a brainstem lesion or a spinal cord lesion had a significantly higher incidence of having an initially remitting course (see fig. 5 for the level of statistical significance). In contrast, those with an initial lesion at more than one site (mixed category, fig. 5) more often had a progressive course from the onset or a tendency to have a cumulative disability following several initial relapses ($P < 0.002$) (fig. 5).

Prognosis and course by duration of initial symptoms. The length for which the initial symptoms lasted could be correlated with the prognosis in the case of 607 patients. A linear and highly significant relationship was noted between the length of the initial symptom and the severity of the disease, irrespective of its nature ($\chi^2 = 227.05$,

TABLE 4 DISEASE PROGNOSIS BY DURATION OF INITIAL SYMPTOMS

Prognostic categories	Duration of initial symptoms (%)							Total
	<1 month	1-3 months	4-6 months	7-12 months	1-2 yrs	3-10 yrs	>10 yrs	
Benign (274)	36.9	22.6	9.1	5.8	1.5	3.3	6.6	100
Moderate (44)	15.9	34.1	4.5	2.3	0	0	27.3	100
Intermediate (90)	20.0	15.6	5.6	6.7	0	2.2	27.8	100
Subacute (114)	25.4	13.2	3.5	1.8	2.6	0	43.0	100
Acute (49)	12.2	8.2	6.1	4.1	0	57.1	2.0	100
Hyperacute (36)	11.1	8.3	8.3	8.3	13.9	41.7	2.8	100
Total (607)	27.2	18.6	6.9	4.9	2.0	8.9	17.5	100

$\chi^2 = 227.05$, $df = 30$, $P < 0.00001$ (analysis based on absolute numbers). In column 1, figures in parentheses are absolute numbers

TABLE 5 DISEASE PROGNOSIS BY INTERVAL BETWEEN ONSET AND FIRST RELAPSE

Prognostic categories	Interval between onset and first relapse (%)					Total
	1-6 months	7-12 months	1-3 yrs	4-5 yrs	>5 yrs	
Benign (232)	17.7	18.1	16.4	10.8	37.0	100
Moderate (38)	0	13.1	15.8	15.8	55.3	100
Intermediate (78)	6.4	15.4	21.8	15.4	41.0	100
Subacute (89)	23.6	15.7	27.0	14.6	19.1	100
Acute (27)	25.9	18.5	37.0	11.1	7.4	100
Hyperacute (24)	29.2	41.7	25.0	4.1	0	100
Total (488)	16.6	18.0	20.7	12.3	32.4	100

Patients from unclassified prognostic category (232), those who died between 1970 and 1980 after a variable disease period (132), those who had a progressive course from the start (95), those with a single episode as well as those in whom the O-R interval was unknown (108) are not shown here. Overall $\chi^2 = 64.607$, $df = 20$, $P < 0.00001$. Absolute numbers in each category are shown in parentheses in column 1.

$df = 30, P < 0.00001$) (Table 4). Of the 274 patients with a benign prognosis, in 36.9% the initial symptoms resolved within 1 month compared with only 11.1% of those in the hyperacute and 12.2% in the acute prognostic categories. In a sizeable majority of the patients in the latter two categories (41.7% and 57.1%, respectively), the initial symptoms did not resolve even by the second year. The earlier the resolution of initial symptoms, the more likely was the disease to stay in remission for a longer period. Of the 311 patients who were in remission, in 41.9% the symptoms had resolved by 1 month compared with 26.8% of the 233 with a relapsing cumulative, 21.4% of the 131 with a relapsive progressive and 1.6% of the 63 with a progressive course.

Onset—first relapse (O—R) interval by prognosis of the disease. The longer the O—R interval, the better the prognosis (Table 5). Of the 232 patients in the benign category, only one-third had the first relapse in less than 1 year compared with 70.9% of those in the hyperacute (category 6) and 44.4% of those in the acute (category 5) prognostic categories. A long O—R interval was also associated with a longer survival, for example, 55.3% of those survived over 20 yrs from the onset (moderate prognostic category) had an O—R interval exceeding 5 yrs.

Prognosis by course of the disease. This correlation was possible in 1036 patients. Of these, 346 patients had a remittent course. These were excluded because in them the prognosis was either benign (51%) or a short follow-up did not allow the prognosis to be judged. In the other three course categories a highly significant difference was noted in the disease prognosis (fig. 6). Of those with a relapsing cumulative course 26% had a benign prognosis compared with 1% of those with relapsing progressive and 4% of those with a progressive course. The proportion of those with an acute and hyperacute prognosis was correspondingly higher in those with a progressive course from the start. The differences were highly significant ($\chi^2 = 412.2, df = 20, P < 0.0001$) (Fig. 6). Mean duration of the disease was also shortest amongst those with a progressive course from the start; details on this aspect have been published elsewhere (Phadke, 1987).

Relationship between the disease course and prognosis and address in childhood or at the onset of the disease, social class and the family history of MS. Residential address in childhood or at the onset of the disease had no relationship with the course or the prognosis of the disease.

Those with a family history of MS frequently had an acute prognosis, but this was not statistically significant. Those with a family history of MS had a significantly greater chance of having a progressive course from the start of the disease ($P < 0.02$) (Table 6).

Social class at the onset of the disease also had a clear relationship with the course and prognosis of the disease (Table 7). Those from social classes I and II frequently had a benign prognosis and a remittent course as compared with those belonging to social classes IV and V who more often belonged to the acute or hyperacute prognostic categories ($\chi^2 = 13.302, df = 4, P < 0.002$), and had a progressive course from the start of the disease ($\chi^2 = 19.4, df = 6, P < 0.03$) (Table 7).

Relationship between VEP P100 latency and disease course and prognosis. VEPs were recorded in 349 patients. Those from the hyperacute or acute prognostic categories more often had a bilaterally delayed VEP P100 latency ($P < 0.05$). Most patients with

TABLE 6 COURSE OF THE DISEASE BY FAMILY HISTORY OF MULTIPLE SCLEROSIS

Family history of MS	Course of the disease*			
	Remittent	Relapsing-cumulative	Relapsing-progressive	Progressive
Present	11.9	15.9	15.5	21.9
Absent	88.1	84.1	84.5	79.1
Total	100 (344)	100 (276)	100 (154)	100 (64)
	Total			
				14.7
				85.3
				100 (838*)

Details for 1 patient unavailable. Values in parentheses are absolute numbers. $\chi^2 = 5.19$, $df = 1$, $P < 0.02$.

TABLE 7. PROGNOSIS AND COURSE BY SOCIAL CLASS AT ONSET OF MULTIPLE SCLEROSIS

Social class	Prognostic categories (%)				Course of the disease (%)		
	Benign	Moderate intermediate and subacute	Acute and hyperacute		R	RC	RP
I, II	33.8	26.9	21.5		32.5	31.3	29.4
III	47.4	40.6	49.2		49.1	43.9	43.4
IV, V	18.8	32.5	29.2		18.4	24.8	27.2
Total	100 (234)	100 (212)	100 (65)		100 (277)	100 (230)	100 (136)
							100 (47)

R = remittent, RC = relapsing-cumulative, RP = relapsing-progressive, P = progressive. Values in parentheses are absolute numbers. Patients who could not be classified in a social class group are not shown. χ^2 for prognosis of the disease = 13.302, $df = 4$, $P = < 0.002$, χ^2 for the disease course = 19.4, $df = 5$, $P < 0.03$.

a moderate intermediate and subacute prognosis had the disease well established for many years before the local availability of the VEP recording facilities. Of the 60 patients from these three categories in whom VEPs were recorded, a very high proportion (83.3%) had a prolonged P100 latency, and in a majority of the cases these changes were bilateral (Table 8). Amongst the various course categories, those with a progressive course (i.e., those with severe disease) also often had bilaterally abnormal VEP P100 latency ($P < 0.002$) (Table 8).

Prognosis and course by changes in the cerebrospinal fluid (CSF). The CSF was examined in 636 patients. Changes in any of the CSF parameters had no relationship with the prognosis or the course of the disease, with the exception of an insignificant excess of those with a remittent course having a CSF pleocytosis.

Brain CT scan findings and disease course and prognosis

Ninety-seven patients had a CT brain scan on a second generation scanner. Of these, 45.6% had one or more than one abnormality such as cortical atrophy, periventricular low density areas, or an enhancing lesion presumed to be MS plaques. The CT scan findings had no significant relationship with the course or the prognosis of the disease.

Worldwide comparison of clinical features of MS

Comparison of the various clinical features between different centres is presented in Tables 9–11. In Table 9, age at onset, sex distribution and disease course have been compared; in Table 10, the pattern of initial symptoms and of the initial anatomical site of the lesion have been compared, and in Table 11, the prognosis in terms of disability over a period of time and the mean period of survival have been compared.

Each study has been ascribed a number. The name of the centre, year of the study, author's name(s) and number of patients involved is shown either in the first or second column of each table. The diagnostic criteria used in each study are shown in the second last column in Table 9, the observation period in the last column in Tables 9 and 11, and the interval between two surveys (wherever they took place) is shown in the last column in Table 11. Studies derived from a hospital source have been designated by 1 asterisk and those derived from an epidemiological source by 2 asterisks.

Age at onset. In most centres the age at onset fell between 20 and 50 yrs. A significantly higher proportion of patients in the eastern hemispheres were, however, reported as having an onset under the age of 20 yrs. Significant differences in the age at onset were also noted amongst the western series (Table 9, column 5). Owing to the possibility of case selection in the hospital-derived series, comparison was restricted to the series derived from epidemiological sources (designated by **); even amongst these, highly significant differences were noted between the various centres ($\chi^2 = 33.64$, $df = 11$, $P < 0.001$).

Sex distribution. Female preponderance was evident in all western series except in study 6 (Table 9, column 6). The proportion of females varied from 53% (study 8) to 71% (study 23). Statistical analysis of the actual numbers, however, showed no significant difference between the various larger series.

TABLE 8. PROGNOSIS AND COURSE BY VEP P100 LATENCY

VEP P100 latency	Prognostic categories*			Disease course**			
	Benign	M+I+S	A+H	R	RC	RP	P
% normal	42.5	16.2	30.0	60.4	37.4	23.1	42.3
% abnormal	57.5	83.8	70.0	39.6	62.6	76.9	57.7
Total	100 (80)	100 (37)	100 (60)	100 (169)	100 (115)	100 (39)	100 (26)
% unilaterally abnormal	32.6	25.8	14.3	49.3	27.8	16.7	13.3
% bilaterally abnormal	67.4	74.2	85.7	50.7	72.2	83.3	86.7
Total abnormal	100 (46)	100 (31)	100 (42)	100 (67)	100 (72)	100 (30)	100 (15)

* M = moderate, I = intermediate, S = subacute, A = acute, H = hyperacute χ^2 for differences between the benign and acute and hyperacute prognostic groups for unilateral vs bilateral P100 delay = 4.056, df = 1, $P < 0.05$. χ^2 for differences in the number of cases with abnormal VEP between the three prognostic categories = 8.249, df = 2, $P < 0.02$. Values in parentheses are absolute numbers ** R = remittent, RC = relapsing-cumulative, RP = relapsing-progressive, P = progressive. χ^2 for differences in the proportions of those with unilateral and bilateral VEP P100 abnormality between the four course categories = 15.21, df = 3, $P < 0.002$. Values in parentheses are absolute numbers.

TABLE 9 COMPARISON BETWEEN WORLD-WIDE CLINICAL PATTERN OF MULTIPLE SCLEROSIS (STUDIES REPORTED BETWEEN 1949 AND 1984)

Study no.	Country and city	Author(s) and year	Total no. of patients	Course of disease										Mean observation period (yrs)
				Age at onset (%)		Sex	Relapsing-remitting	Progressive	Relapsing-progressive	Diagnostic criteria				
				<20	20-50						F	M		
1	Sweden (Stockholm)*	Muller (1949)	793	22	77	1	56	44	87	13	—	Self-devised	9.7	
2	UK (London)*	McAlpine and Compston (1952)	840	12	85	3	65	35	65	10	25	Self-devised	11.3	
3	Northern Ireland (Belfast)**	Allison and Millar (1954)	700	8	87	5	56	44	—	—	—	Self-devised	—	
4	Denmark (nationwide)**	Hyllsted (1956)	2731	12	81	1	55	45	—	—	—	Self-devised	10+	
5	Canada (Manitoba)**	White and Whealan (1959)	68	18	80	2	57	33	75	24	—	Self-devised	—	
6	Holland (Groningen)**	Dassel (1960)	265	9	90	1	48	52	—	—	—	Self-devised	—	
7	UK (Northumberland)**	Poskanzer et al. (1963)	636	—	—	—	58	42	—	—	—	Allison and Millar	11.6	
8	Israel**	Leibowitz et al. (1964)	266	15	77	8	53	47	67	33	—	Allison and Millar	11.5	
9	Norway (Vestfold)**	Ofthel (1966)	127	9	86	5	56	44	—	—	—	Allison and Millar	14.3	
10	Korea*	Kurtzke et al. (1968a)	44	25	75	—	25	75	78	22	—	Schumacher	3.3	
11.	USA (male war veterans)	Kurtzke et al. (1968b)	527	16	84	0	—	100	—	—	—	Self-devised	4.7	
12	Finland (Turku)**	Pandius (1969)	146	18	81	1	61	39	90	10	—	Allison and Millar	12.9	

13.	Iceland (nationwide)**	Gudmundsson (1971)	94	21	79	—	63	37	86	14	—	Schumacher	24.3
14.	India (Vellore)*	Mathew <i>et al.</i> (1971)	60	15	85	—	32	68	80	20	—	Schumacher	4.2
15.	Japan (nationwide)**	Kuroiwa <i>et al.</i> (1975)	1084	26	68	6	57	43	67	33	—	Modified Schumacher	—
16.	Taiwan*	Hung <i>et al.</i> (1976)	25	24	64	12	76	24	84	16	—	Schumacher	1-13
17.	France (Lyon)*	Confavreux <i>et al.</i> (1980)	349	11	83	6	60	40	58	24	18	McAlpine	9.0
18.	UK (London)*	Shibasaki <i>et al.</i> (1981)	204	—	—	—	66	34	64	5	31	McDonald and Halliday	1-7
19.	Sweden (Göteborg)**	Broman <i>et al.</i> (1981)	312	10	86	4	61	39	—	—	—	Self-devised	13-27
20.	W Germany (Lower Saxony)**	Pöser <i>et al.</i> (1982a,b)	221	10	90	—	65	35	59	13	28	Self-devised	16+
21.	Belgium (Melsbroek)*	Vergans <i>et al.</i> (1983)	200	16	81	3	52	48	12	26	62	Schumacher	13.5
22.	Canada (Ontario)*	Noesworthy <i>et al.</i> (1983)	838	16	79	5	67	33	52	24	24	Modified Rose	11.8
23.	USA (Los Angeles and Washington)**	Vlacher <i>et al.</i> (1984)	941	—	—	—	71	29	—	—	—	Modified Schumacher and McAlpine	10-20
24.	UK (NE Scotland)**	Present study	1055	7	80	11	65	35	67	9	22	Modified Allison and Miller	16.5

* In column 2 = studies based on hospital-attending patients only. ** In column 2 = studies based on patients from an epidemiological sample. — = Data for the item is either not mentioned or not clearly indicated in that publication. In study 2, 42 cases from a purely male source of referral have been excluded. In study 14, 9 cases with isolated retrobulbar neuritis have been excluded. Age at onset was unknown in 6% in study 4 and 2% in study 24; disease course was uncertain in 2% in study 24.

TABLE 10 COMPARISON BETWEEN WORLD-WIDE CLINICAL PATTERN OF MULTIPLE SCLEROSIS STUDIES REPORTED BETWEEN 1949 AND 1984

Study no (and source)	Author(s) (yr) (no. of cases)	Pattern of initial symptoms (some indicated as site of lesion) (%)										Distribution by initial site of lesion in the CNS (%)				
		Optic Brain-Cranial Cere- Pyramidal					Sensory Urinary Cerebral Optic					Myelo- Brain- Cere-				
		Cerebral neuritis stem nerves bellar					bellar					stem bellar Spinal Mixed Uncertain				
		5	20	24	24	23	32	22	5	10	17	0	7	0	45	15
1	Muller (Sweden, (1949)	5	20	24	24	23	32	22	5	10	17	0	7	0	45	15
2	Stockholm)* (793) Allison (UK, (1950)	12	17	7	-	12	67	15	0	10	17	0	7	0	45	15
3	N Wales)** (40) White and Wheelan (1959)	-	19	18	-	9	30	16	7	-	-	-	-	-	-	-
4	(Canada, Kingston)** (59) McAlpine (UK, (1961)	?	29	?	?	7	39	41	-	-	-	-	-	-	-	-
5	London)* (241) Poock and Markus (1964)	-	-	-	-	-	-	-	-	0	7	0	11	3	41	38
6	Freiburg)* (195) Ofstedel (Norway, (1966)	3	24	8	-	0	55	7	0	-	-	-	-	-	-	-
7	Vestfold)** (127) Leibowitz and Alter (1973)	10	14	14	15	8	38	13	2	-	-	-	-	-	-	-
8	(Israel, nationwide)** (263) Kuritzin <i>et al.</i> (USA, war veterans)* (527)	13	31	39	-	44	52	42	14	?	?	?	?	?	?	?

[illegible]

* Studies on hospital-derived sample only **Studies on patients from an epidemiological source. — = Data on these variables not available. ? = Available data unclear.
† = also includes cases with brainstem symptoms.

† = also includes cases with brainstem symptoms.

TABLE 11. COMPARISON OF THE DISEASE PROGNOSIS (DISABILITY BY DURATION OR DURATION UNTIL DEATH) BETWEEN VARIOUS PUBLISHED SERIES

Study no.	Source, author(s), nature of study, Total no. of cases, deaths	Prognostic categories (% of total)				Mean duration of disease up to death (yrs)	Disability grading used	Interval*** between surveys (S1-S2) or period under consideration
		Benign	Intermediate	Severe	Dead	Unclassified		
1*	Edinburgh, Bramwell (1917) prospective, 200	-	-	-	-	-	None	? period
2*	Germany, Curtius (1933), retrospective, 100	-	-	-	-	-	None	? period
3*	Denmark, Graum (1934), retrospective, 689, 250 deaths	-	-	-	-	-	None	? period
4*	London (UK), Braum (1936), retrospective, 171, 11 deaths	-	-	-	-	-	None	? period
5*	Germany, Viertheilug (1940), retrospective, 141	8	32	28	31	-	Working ability	1920-1935
6*	Sweden, Sallstrom (1942), retrospective + reexamination after 10 yrs, 1365, 285 deaths	-	-	-	-	-	None	1926-1934
7*	Sweden, Muller (1949), retrospective + reexamined, 810, 190 deaths	26	22	28	24	-	Mobility with or without aid	1920-1945
8**	North Wales, Allison (1950), reexamination of prevalence sample, 40, 20 deaths	-	-	-	-	-	None	S1-S1 = 20 yrs

9**	Boston (USA), Ipsen (1950), field survey, 784	—	—	—	—	—	—	M = 17.5, F = 15.5 (Predicted mortality)	None	1939–1948
10*	New York, Carter <i>et al.</i> (1950), retrospective selected autopsy series, 46	—	—	—	—	—	—	13	None	Autopsy series, 1909–1946
11*	Rochester (Mayo Clinic) USA, Lazarie (1950), retrospective, 342, 85 deaths	—	—	—	—	—	—	Non ambulatory = 13.7 Ambulatory = 15.5	Mobility at initial assessment	1915–1944
12*	Würzburg (Germany), Abb <i>et al.</i> (1956) retrospective + reexamination, 1420, 684 deaths, disability by duration known in 958 patients	13	32	20	25	10	—	11	Employment ability at review or death by the time of review	1935–1952
13*	London (UK), McAlpine (1961) prospective, 241, 83 deaths	32	33	?	34	—	—	11	Self-devised grading	S1-S2 = 10 yrs 1949–1959
14**	Denmark, Hyllsted (1961), retrospective and prospective, 2731, 854 deaths	—	—	—	—	—	—	25–29		S1-S2 = 10 yrs
15**	N Ireland, Gruber (1962), follow-up of a prevalence sample, 698, 229 deaths	32	27	8	33	—	—	—	Hyllsted	S1-S2 = 10 yrs
16*	Paris, Boudelle <i>et al.</i> (1962), retrospective, 145	8	?	20	7	65	—	—	Undefined	?

Study no	Source, author(s), nature of study, Total no of cases, deaths	Prognostic categories (% of total)				Mean duration of disease up to death (yrs)	Disability grading used	Interval*** between surveys (S1-S2) or period under consideration
		Benign	Intermediate	Severe	Dead			
17*	Freiberg (W Germany), Poeck <i>et al.</i> (1964), 195	9	39	?	52	—	McAlpine	1940—1962
18**	Winnipeg, Stazio <i>et al.</i> (1964), prevalence sample + follow-up, 149, 40 deaths	—	—	—	—	17.7	None	S1-S2 = 10 yrs
19**	Vestfold (Norway), Ofstedal (1966), point prevalence sample, 127	24	36	12	Not incl. in stats	28	Hyllsted	Single point survey
20**	Romsdal (Norway), Preslhus (1962), point prevalence sample, 81	37	37	10	Not incl. in stats.	16	Hyllsted	Single point survey
21**	Israel, Leibowitz and Alter (1973), point prevalence sample, 266	21	29	20	30	17.4	Hyllsted	S1-S2 = 7 yrs
22*	Rochester, Percy <i>et al.</i> (1971), prevalence sample, 67	55	20	—	25	25	Ambulant vs non ambulant	S1-S2 = 20 yrs
23*	Iceland, Gudmundsson (1971), prevalence sample + resurvey, 83, 20 deaths	66	?	10	24	24.1	Hyllsted + McAlpine	S1-S2 = 14 yrs
24*	Toulouse (France), Ruser <i>et al.</i> (1971),	15	35	31	19	—	Self-derived	10—40 yrs observation

		23	40	30	7	—	Estimated 30 yrs	Kurtzke	S1-S2 = 10+ yrs
25*	retrospective, 203, 39 deaths USA, male veterans, Kurtzke <i>et al</i> (1977), all MS patients seen over a specified period, 527 (442 followed for 10 yrs +)								
26*	Lyon (France), Confavreux <i>et al</i> (1980), quasi-prospective, 349, 20 deaths	14	10	16	Not incl. in stats.	60	Female = 13 1 Male = 9 0	McAlpine	1957-1976
27**	Göteborg (Sweden), Broman <i>et al.</i> (1981, 1982, unpublished), prevalence sample and prospective follow-up, 312, 49 deaths	25	46	13	16	—	—	Self-derived	13-27 yrs observation
28**	Lower Saxony (W. Germany), Poser <i>et al.</i> (1982a), point prevalence sample, 282	11	29	16	Not incl	44	—	Kurtzke	Single point survey
29**	Los Angeles (USA), Visser <i>et al.</i> (1984), follow-up of a prevalence sample, 941	40	?	45	15	—	—	Self-derived	S1-S2 = 10 yrs
30**	Present study, analysis of a group seen between 2 prevalence studies, 1055, 216 deaths	26	23	8	21	22	M = 23.5, F = 25.7	McAlpine	S1-S2 = 10 yrs

* In column 1 = a hospital based study ** In column 1 = study based on an epidemiological sample. *** This column indicates period between 2 surveys for samples derived from epidemiological source or calendar years between which patients were included in the retrospective analysis.

Course of the disease. Comparison on this aspect proved particularly difficult because of lack of uniformity in the definitions of the different course patterns (Table 9, column 7). In 16 studies data on this aspect were available. Of these, in 9 the patients were grouped under two course categories, namely remittent-relapsing and progressive; in the remaining 7, an additional third category of a relapsing-progressive course was identified. In the first of these two former groups (of 9 series) the proportion of patients with a progressive course ranged between 10 and 33%. Confining the statistical analysis to this group also showed a highly significant difference in the proportion of cases with a progressive course from the onset ($\chi^2 = 32.1$, $df = 5$, $P < 0.0001$). In the second group of 5 series, the proportion of patients in the three categories also differed highly significantly ($P < 0.001$). A significant difference in the proportion of cases in the various course categories was also noted in the hospital-derived series (*) ($P < 0.04$).

Pattern of initial symptoms. This aspect could be compared between 18 series (Table 10). Nonspecific symptoms such as headache, fatigue, etc., were excluded from the present comparison. The high frequency of initial symptoms due to optic neuritis in the eastern centres is obvious from the values in Table 10. In several other eastern studies not shown in Table 10 a similar high frequency was also observed (Kurtzke *et al.*, 1968a; Baoxun *et al.*, 1982; Vejajiva, 1982).

On comparing the frequency of symptoms due to lesions in the brainstem, pyramidal tracts, sensory tracts, cerebellum and of urinary control, highly significant differences were noted between different centres (Table 10). These differences remained highly significant despite comparing separately the hospital-based with the epidemiologically-derived series ($P < 0.03$ to < 0.005).

Distribution of the initial anatomical site of lesion in the central nervous system. This was adjudged by combining the neurological signs and symptoms. Only in 4 series with a sufficiently large patient sample (studies 2, 5, 13, 18) could this aspect be compared (Table 10). The high frequency of initial unilateral or bilateral optic neuritis noted in Taiwan (study no. 13) is strikingly obvious. Other studies from the east not shown in Table 10 have revealed similar findings (Gouri-Devi and Nagaraja, 1982; Renales *et al.*, 1982; Vejajiva, 1982). A significant difference was also noted in the frequency of lesions at other sites. In the present series (study no. 18, Table 10), a high frequency of an initial brainstem lesion was noted compared with the Welsh and the West German series. In contrast, in the German series (study no. 5), a higher number of patients seemed to have initial lesions at multiple sites. Similar data from other centres with unselected patient samples are needed before firm conclusions on this aspect of the disease can be drawn.

Prognosis of the disease

The degree of disability over a period of time (often analysed retrospectively) was known for 30 series, and the mean duration between onset to death was known for 21 centres. On comparing the 10 series derived from epidemiological sources separately (designated by **) a highly significant difference was noted ($P < 0.005$). On splitting these 10 series into three groups, i.e., those where the prognosis was assessed between two prevalence surveys (Table 11, studies 15, 21–23, 29, 30), those where it was assessed retrospectively at a point prevalence study (study nos. 19, 20, 28), and thirdly,

those where it was assessed prospectively (study no. 22), a highly significant difference was noted in the severity of the disease in each of the three groups.

On comparing separately the hospital-based series (designated by an asterisk in Table 11) a significant difference in the prognosis of the disease in patients from different centres was also noted ($P < 0.005$). In keeping with the generally held belief, the proportion of cases in the benign category was generally lower in the hospital-derived group (range 8–32%), and that in the severe category was generally higher (range 16–31%) compared with most of the epidemiologically-derived samples.

The mean period of survival (the interval between onset and death) was known for patients from 21 centres. This was less than 15 yrs in most studies from the preantibiotic era. Series published in the last 30 yrs showed widely diverse figures ranging from 17.4 yrs (study 2, Table 11) to 29 yrs (study 14); the majority of the studies in this period, however, showed a mean survival period around 25 yrs with the exception of those from Winnipeg (study 18) and Israel (study 2) where a reason for a shorter survival period is not apparent.

In the solitary eastern study, where mortality amongst 256 Chinese patients was analysed retrospectively, a much more severe prognosis was noted (Baouxun *et al.*, 1982). In this group, of the 19 patients who died during the observation period ranging between 7 and 30 yrs, 11 died within 2 yrs of onset; of those who were alive, all those remaining, apart from 5%, became moderately to severely disabled within 10 yrs of onset. These figures support the generally held belief that MS in the eastern hemisphere has a more severe prognosis as compared with the west; this, however, needs confirmation with data from other eastern centres.

DISCUSSION

As noted in Table 11, duration of the disease, disability at a point in time, or disability between two surveys have all been used as measures of the severity of the disease. More recently, disability at a point in time combined with disease duration has been used as a 'disability index' to assess the prognosis (Poser *et al.*, 1982a; Verjans *et al.*, 1983; Visscher *et al.*, 1984). With the exception of a few studies (Allison, 1950; Gruber, 1962; McAlpine, 1964; Leibowitz and Alter, 1973; Kurtzke *et al.*, 1977; Confavreux *et al.*, 1980), most studies have been retrospective, often involving selected and small numbers of patients, usually followed in a hospital because of the severe nature of the disease.

Every system of evaluation has some drawback. Ideally, a longitudinal follow-up of a large cohort of an unselected sample observed from the onset to death would probably give the best idea of disease prognosis. However, the logistics of such an exercise are phenomenal and are usually beyond the scope of a general neurological department. The present study, constituting a close follow-up of an epidemiological sample identified in a prevalence survey, is the closest approach to this ideal. The prognostic classification of Confavreux *et al.* (19980) was found to be well suited to deal with a particularly large sample such as this. Although McAlpine's disability grading system gives only a broad and overall view of the degree of disability, it was found to be simple and reliable, and particularly well suited for obtaining information about the current disability status of the present sample through a postal survey of the general practitioners of the region.

Attempts to identify genetic or immunological host factors which could predict the natural history of the disease have not been fruitful. However, various clinical features of the disease which could predict the course and prognosis have been evaluated. Amongst these, age at onset, sex, and pattern of symptoms at the onset have received the greatest attention. In the present study a number of additional features were analysed, some of which were of predictive value. The following features were associated with a good prognosis: younger age at onset; negative family history of MS; higher social class; certain initial features such as the occurrence of a brainstem lesion or optic neuritis; shorter duration of the initial symptoms; a longer interval between the initial symptoms and the first relapse; and normal or only unilaterally prolonged VEP P100 latency. The prognosis was also significantly better in those with an initially remittent course. Factors which proved to be of no predictive value were sex, address in childhood or at the onset of the disease, changes in the CT brain scan, and CSF findings, including percentage IgG concentration.

The better prognosis associated with a younger age at onset has been noted by the majority of authors (Müller, 1949; Ipsen, 1950; Hyllested, 1961; Poeck and Markus, 1964; Stazio *et al.*, 1964; Bonduelle, 1967; Gudmundsson, 1971; Riser *et al.*, 1971; Leibowitz and Alter, 1973; Kurtzke *et al.*, 1977; Confavreux *et al.*, 1980; Broman *et al.*, 1981; Clark *et al.*, 1982; Poser *et al.*, 1982b; Noseworthy *et al.*, 1983; Verjans *et al.*, 1983; Visscher *et al.*, 1984; Thompson *et al.*, 1986). What is the likely basis of this age-related difference in the prognosis? It is possible that this may just be a function of ageing, as observed, for example, in the context of cerebrovascular disease. Another possibility is that it reflects age-related differences in the behaviour of the immune system. Alteration of T cell function in MS has been demonstrated (Compston, 1983) but age-related differences have yet to be analysed and may prove to be of interest.

Age also clearly influences the course of the disease. The finding in the present study that older patients more often have a progressive course from the start is in keeping with observations in most centres (McAlpine and Compston, 1952; Poeck and Markus, 1964; Leibowitz and Alter, 1973; Confavreux *et al.*, 1980; Poser *et al.*, 1982b; Thompson *et al.*, 1986). In addition, amongst these patients there was also a clear trend of early entry to the progressive phase after an initially relapsing-remitting pattern. Müller (1949), in his retrospective analysis, also observed a similar relationship.

The lack of a significant influence of the patients' sex on the prognosis of the present sample has been observed previously by many (Müller, 1949; Hyllested, 1956; Panelius, 1969; Gudmundsson, 1977; Broman *et al.*, 1981; Visscher *et al.*, 1984).

As in the present series, Müller (1949), Abb and Schaltenbrand (1956), McAlpine (1961), Poeck and Markus (1964) and Panelius (1969) also found a more benign prognosis after an initial brainstem lesion, and Abb and Schaltenbrand (1956), McAlpine (1961) and Wikström *et al.* (1980) have also noted a similar association with an initial optic nerve lesion. Leibowitz and Alter (1973), however, found an opposite pattern with regard to the latter; no explanation for this discrepancy was given. A relationship between a benign prognosis and initial sensory symptoms has also been noted by several other authors (Poeck and Markus, 1964; Gudmundsson, 1971; Riser *et al.*, 1971; Poser *et al.*, 1982b; Visscher *et al.*, 1984).

A poor prognosis has also been reported previously in those with an initial cerebellar

lesion (Müller, 1949; Bonduelle and Albaranes, 1962; Stazio *et al.*, 1964; Gudmundsson, 1971; Kurtzke *et al.*, 1977; Poser *et al.*, 1982b; T. Broman, personal communication), a spinal cord lesion (Abb and Schaltenbrand, 1956; Poser *et al.*, 1978), or lesions at multiple sites in the nervous system (Miller, 1949; Müller, 1949). As shown by others, symptoms indicative of a pyramidal tract lesion also correlated with a poor prognosis in the present study (numerical data not shown). Other symptoms which were associated with a poor prognosis, as shown by a significantly reduced survival in the part of the present sample which was observed until death, included psychiatric and urinary symptoms either at the onset or within the first 10 yrs (Phadke, 1987).

Duration of the initial symptoms had a linear relationship with the disease severity. Kurtzke *et al.* (1977), during the initial analysis of their sample, also noted a similar pattern.

An inverse relationship between the prognosis and the onset to first relapse interval (O-R), as noted in the present sample, has also been observed by many others (Bonduelle and Albaranes, 1962; Riser *et al.*, 1971; Kurtzke *et al.*, 1977; Confavreux *et al.*, 1980; Thompson *et al.*, 1986). Confavreux *et al.* (1980) found a mean O-R interval of 2.4 yrs in those with severe (acute) and 0.9 yrs in those with a hyperacute prognosis; in contrast, the mean O-R interval was 5.6 yrs in their benign cases.

There is almost universal agreement that patients with a progressive course from onset have a poor prognosis (Müller, 1949; Lazarte, 1950; Thygesen, 1953; White and Wheelan, 1959; McAlpine, 1961; Poeck and Markus, 1964; Bauer *et al.*, 1965; Bonduelle, 1967; Confavreux *et al.*, 1980; Noseworthy *et al.*, 1983; Verjans *et al.*, 1983). In the present investigation, a poor prognosis was shown not only by an early severe morbidity but also by a significantly short survival in that part of the present sample which was observed until death (Phadke, 1987).

Correlating the CSF changes with prognosis and course of disease has proved difficult for a number of reasons (Phadke, 1985), particularly the variable association between elevated cell counts and relapse (which at times may be clinically undetectable), the rise in the CSF protein content at the time of a relapse, and the fluctuation in the CSF IgG content and pattern of oligoclonal IgG bands at different times of the disease. Technical factors might also have been responsible for the differences between some centres. In the present study, timing of the lumbar puncture was not precisely recorded in all cases but, in general, CSF was examined during a relapse. The lack of relationship between the level of IgG (expressed as a percentage or an index), and the prognosis of the disease has also been observed by many others (Bergmann *et al.*, 1964; Bradshaw, 1964; Bauer *et al.*, 1965; Kurtzke *et al.*, 1972; Schmidt *et al.*, 1977; Christensen *et al.*, 1978; Paty *et al.*, 1979; Confavreux *et al.*, 1980; Hutchinson *et al.*, 1983; Rocchelli *et al.*, 1983; Thompson *et al.*, 1986). Some authors, however, have reported a close association between raised CSF IgG concentrations and a poor prognosis (Yahr *et al.*, 1954; Olsson *et al.*, 1976; Stendhal-Brodin and Link, 1980; Verjans *et al.*, 1983). The CSF changes in the present series were unrelated to the course of the disease, except that patients with a relapsing disease had a slight but insignificantly greater cell count in their CSF.

In a recent study from Ireland, a lack of relationship between VEP P100 latency and disease prognosis was noted in a group of 70 hospital-attending MS patients (Thompson

et al., 1986). If the significant relationship noted in the present study between a poor prognosis, a progressive course from onset and bilateral prolongation of P100 latency is confirmed, it might prove to be a useful indicator of prognosis.

The present comparison of the clinical pattern of MS in various parts of the world, in particular with regard to the age at onset, the pattern of initial symptoms, and the course and prognosis of the disease, clearly showed that differences exist not only between the eastern and western centres but also amongst the various western centres. While these clinical differences may partly be due to nonuniformity in the selection criteria, taking the entire evidence into account they do seem real. Histological differences in the CNS lesions between Caucasian and Oriental MS patients have been reported (Ikuta *et al.*, 1982). Two possibilities arise. The difference might be due to a variation in the genetic or immunological make-up as shown by differences in the HLA characteristics of MS patients from various parts of the world (Batchelor, 1985), or the disease clinically identified as MS may be triggered by several different, as yet unidentified, environmental factors in different parts of the world. Further studies on comparable patient samples might prove to be of value.

In conclusion, analysis of this large unselected series of MS patients closely observed in a region under epidemiological investigation has provided valuable information about the course and prognosis of the disease and the factors influencing them. The significance of a number of previously identified prognostic factors has been confirmed and several new ones identified. The reasons for the clinical differences in different parts of the world remain uncertain and their elucidation may throw light on the aetiology of the disease.

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CONGENITAL DEMYELINATING MOTOR AND SENSORY NEUROPATHY WITH FOCALLY FOLDED MYELIN SHEATHS

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SUMMARY

Six patients (5 index cases and 1 sib) with a congenital motor and sensory neuropathy are described. The clinical, genetic and electrophysiological features resembled Dejerine-Sottas disease or hereditary motor and sensory neuropathy (HMSN) type III. Sural nerve biopsy of 5 patients revealed segmental demyelination and remyelination with hypertrophic changes, although onion bulbs were not as ubiquitous as in classical HMSN type III. A striking discriminating feature from HMSN type III was an abundance of focal myelin thickenings (tomacula) present in nearly all teased fibres. Possible pathogenic implications are discussed. These cases corroborate the heterogeneity of congenital motor and sensory neuropathies.

INTRODUCTION

The congenital and infantile motor and sensory neuropathies constitute a heterogeneous group of disorders with an onset before the age of 2 yrs. The nosology is still a matter for discussion (Harding and Thomas, 1980; Guzzetta *et al.*, 1982; Hagberg and Westerberg, 1983; Lütschg *et al.*, 1985). Besides classical Dejerine-Sottas disease or hereditary motor and sensory neuropathy (HMSN) type III characterized by hypomyelination and prominent onion bulb formation (Dyck, 1975; Ouvrier *et al.*, 1987) this group includes cases with severe hypomyelination and atypical onion bulbs (Lyon, 1969; Joosten *et al.*, 1974; Kennedy *et al.*, 1977; Guzzetta *et al.*, 1982) and cases without myelin and no onion bulbs (Karch and Urich, 1975; Palix and Coignet, 1978; Charnas *et al.*, 1988). In addition, patients with HMSN type II (Ouvrier *et al.*, 1981; Hagberg and Westerberg, 1983) or with dominantly inherited HMSN type I (Vanasse and Dubowitz, 1981) may be affected from birth. Occasionally, early infantile onset of a chronic or relapsing inflammatory demyelinating polyneuropathy has been described (Chambers and MacDermot, 1957; Pasternak *et al.*, 1982; Gabreëls-Festen *et al.*, 1986).

Recently, attention has been drawn to the morphological phenomenon of focal myelin thickenings in some rare cases of congenital demyelinating motor and sensory neuropathy (Nordborg *et al.*, 1984; Lütschg *et al.*, 1985; Vallat *et al.*, 1987; Vital *et al.*, 1987).

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In the course of 19 yrs we have investigated 27 patients with a congenital demyelinating motor and sensory neuropathy. In this group were 5 patients with congenital demyelinating motor and sensory neuropathy in which focal myelin thickenings (tomacula) were an impressive feature of sural nerve morphology. Our present Case 3 was published briefly as a morphologically distinct type of idiopathic infantile chronic demyelinating neuropathy (Joosten *et al.*, 1977).

CLINICAL FEATURES

Five patients with congenital motor and sensory neuropathy, in whom sural nerve biopsy revealed numerous focal myelin thickenings (tomacula) on almost every teased fibre, are included in this report (Table 1). The clinical and electrophysiological data of 1 affected sib are added (Case 4b).

TABLE 1. CLINICAL SIGNS AND SYMPTOMS

	Case					
	1	2	3	4a	4b	5
Age at first examination (yrs)	2	3	14	26	28	47
Sex	F	M	F	F	M	F
Onset (yrs)	Birth	<1	0.25	Birth	<1	<1
Age of walking (yrs)	3	2.5	2.5	4*	2	?
Wheelchair-dependent (yrs)	—	—	—	+(12)	—	±
Pes cavus	+	+	+	+	+	+
Scoliosis (onset, yrs)	—	—	+(10)	+(13)	+(12)	+
Muscle weakness						
Distal leg	+	+	+	++	++	++
arm	±	±	+	++	+	+
Proximal leg	±	—	—	++	+	+
arm	—	—	—	+	—	—
Muscle atrophy						
Distal	±	±	—	++	+	+
Proximal	—	—	—	+	±	+
Hypotonia	+	±	+	+	+	+
Areflexia	+	+	+	+	+	+
Ataxia	+	+	+	+	+	+
Vibration-position sense	?	?	+	+	+	+
impairment						
Pain-temperature sense	?	?	+	+	—	+
impairment						
Clinically enlarged nerves	—	—	—	—	—	—

* Walking with support. — = absent, ± = slight; + = marked, ++ = severe.

Early symptoms were noticed at birth or in the first year of life. Two patients were floppy at birth. In all cases motor milestones were severely delayed. Walking was not acquired before the end of the second year of life by all patients and gait remained clumsy and stumbling. Case 4a was never able to walk unsupported. At the age of 12 yrs she became wheelchair dependent. Her brother (Case 4b) had progressive walking difficulty until adolescence, but is still ambulant at 38 yrs. Pes cavus was noted early in all cases. During early puberty scoliosis developed, and necessitated surgery in Case 3. Pressure palsies were not experienced by any patient or by their relatives.

At the first clinical examination all patients showed hypotonia and weakness, especially of distal limbs, the legs being more affected than arms. The adult patients also had proximal weakness. Tendon reflexes were absent. Atrophy was absent or slight in the 3 youngest patients; Case 3 even had slightly enlarged

calves. Ataxia was evident in all patients. An impairment of vibration and position sense, and to a lesser degree of pain sensation, was present in the 4 eldest patients. Thickened nerves were not found in any patient. In Case 5, pupillary response to light was decreased and a slight perceptive hearing loss was present. The others had normal cranial nerve function.

Laboratory findings are summarized in Table 2. CSF analysis in 4 patients showed normal cell counts. The protein content was normal in the infants and elevated in Cases 3 and 5. Motor conduction velocity was severely reduced, ranging from 2 to 11 m·s⁻¹ in the median nerve. Sensory action potentials were absent. Activity of leucocyte arylsulphatase A and serum phytanic acid content were normal.

No consanguinity was known to the parents in any family. Parents and sibs (n = 9) of 4 of our 5 index cases were examined clinically and electrophysiologically. They were normal with the exception of 1 affected brother (Case 4b). The parents of Case 5 were normal by history; 1 of the sibs was said to suffer from a similar disorder.

TABLE 2 LABORATORY FINDINGS

	Case					
	1	2	3	4a	4b	5
Median MNCV (m·s ⁻¹)	7	11	8	2	10	3
CSF protein (g/l)	0.35	0.41	0.65	—	—	1.52
(normal <0.45 g/l)						

FOLLOW-UP OBSERVATIONS (Table 3)

The length of the follow-up was 0.5–16 yrs, mean 9.5 yrs. Progression was slow in all cases. After puberty progression was barely noticed either by the patients or by their close relatives. Only after careful interrogation did they become aware of a slight progression during an interval of many years. Case 1, at the age of 9.5 yrs, developed scoliosis. The adult patients all had proximal weakness of the legs, yet Case 4b was able to walk several kilometres. Cases 3 and 4a also had slight proximal weakness in the arms. The adults showed acrocyanosis of the lower legs. They were of short stature in adult life. Case 5 died at the age of 63 yrs due to cardiopulmonary disturbances. From the age of 50 she had used a wheelchair, but up to her death she had been able to knit and to dress herself.

TABLE 3 FOLLOW-UP OBSERVATIONS

	Case					
	2	1	3	4a	4b	5
Age at last investigation (yrs)	3.5	9	27	36	38	63 [†]
Age at first investigation (yrs)	3	2	14	26	28	47
Follow-up (yrs)	0.5	7	13	10	10	16
Progression of:						
Muscle weakness	0	0	>>	>	>	>
Muscle atrophy	0	>	>>	>	>	>
Sensory deficit	0	>>	>	>	>	>
Scoliosis	0	>	Fixed	0	0	0
Wheelchair-bound	—	—	—	+12 yrs	—	+50 yrs
Maximum walking distance (km)	0.5	1.0	0.3	—	10.0	—
Height (cm)*	103	135	155	148	150	Low normal

* Cases 1 and 2 between 40th and 60th centile, Case 3 <10th centile, Cases 4a and 4b <2.5 centile for age and sex. Progression 0 = absent; > = inconspicuous; >> = slight. [†]Deceased.

MATERIAL AND METHODS

Whole sural nerve biopsy was performed at midcalf level and prepared for light and electron microscopic examination, including teased fibre studies, using standard techniques.

The total transverse fascicular area was determined with the aid of a planimeter on photographic enlargements of semithin sections of the nerve. Electron microscopic photographs ($\times 1700$) covering approximately 10% of the total transverse fascicular area were used for morphometric analysis. The density of myelinated fibres and their external and axonal diameter were determined using a Zeiss TGZ 3 particle size analyser. Myelinated fibres were considered as all those nerve fibres presumed to belong to the myelinated fibre group, namely axons with myelin, and those of larger diameter ($> 1.7 \mu\text{m}$) without myelin but surrounded by one or more extra Schwann cell processes (non or demyelinated fibres) (Guzzetta *et al.*, 1982). The total number of myelinated fibres and of non or demyelinated fibres was calculated as the product of the total transverse fascicular area and the respective densities. The g ratio (axon diameter/total fibre diameter) was determined in each nondegenerating fibre presumed to belong to the myelinated fibre group; g ratio was plotted against the corresponding axon diameter and not against fibre diameter, as is often done. From each nerve at least 50 single myelinated fibres were teased, with the exception of Case 5 in which only 8 myelinated fibres were left in the fascicle available for teasing. Teased fibres were classified according to Dyck *et al.* (1984) for paranodal or segmental de and remyelination and for the presence of one or more focal myelin thickenings.

RESULTS

Light microscopy

In the semithin transverse sections almost all myelinated fibres appeared abnormal. The majority was without myelin or only thinly myelinated. A substantial number of fibres, however, had extremely thick myelin sheaths (fig. 1). Longitudinal sections and teased fibres showed many focal spherical or cylindrical tomaculous myelin thickenings (fig. 2). Onion bulb formations were present in varying degrees in all patients.

Electron microscopy

On ultrastructural examination, the tomacula appeared similar to those depicted by Madrid and Bradley (1975) in hereditary liability to pressure palsies (HLPP), particularly redundant loop formation. Both external loops, internal loops and intramyelin folds were seen. The loops were wrapped around the entire axon or were coiled up next to the axon (figs 3, 4). In longitudinal sections excessive folded myelin sheaths appeared to pass into thin myelin sheaths along the same internode. Sometimes the tomacula extended from the node of Ranvier to the nucleus of the Schwann cell (fig. 4). The myelin structure of the tomacula in our patients had been preserved excellently in the ultrathin sections. This is in contrast to the frequently observed preparative artefacts of HLPP tomacula (Behse *et al.*, 1972; Van Wensen, 1980; Meier and Moll, 1982). Occasionally, complex partially degenerating tomacula were seen. The axon within the tomacula usually did not show signs of compression. In the children, most tomacula were not surrounded by extra Schwann cell whorls or redundant basement membranes; in the adults tomacula usually were inside small onion bulb structures.

Onion bulb formation was present in all cases, but it was not as ubiquitous as in classical HMSN type III (Dyck, 1975; Ouvrier *et al.*, 1987). In the children onion bulbs were composed either of double layered basement membranes or a few concentric layers of

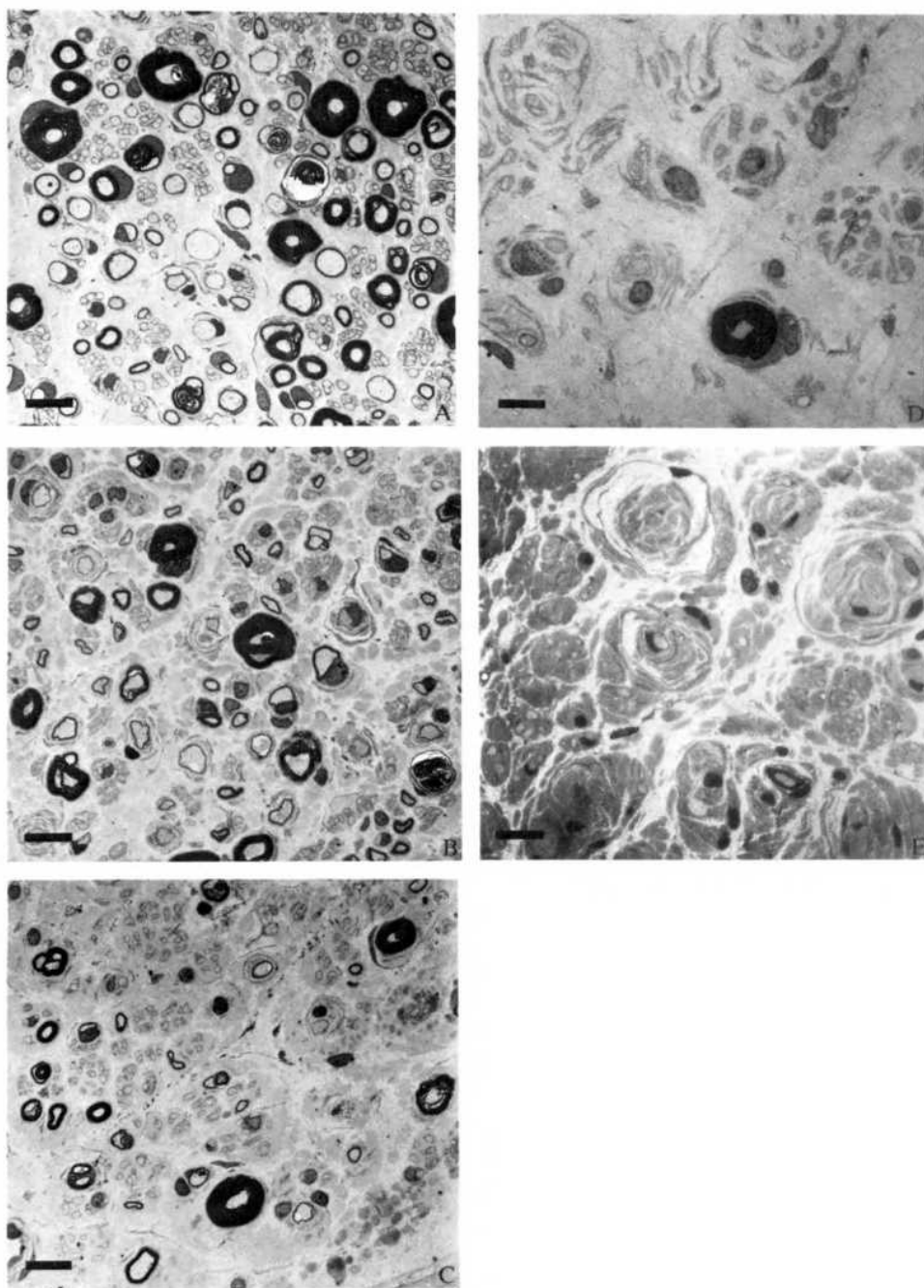


FIG. 1. Low power electron microscope picture of cross-sections of sural nerve biopsies. A, Case 1 (aged 2 yrs); B, Case 2 (aged 3 yrs); C, Case 3 (aged 14 yrs); D, Case 4a (aged 26 yrs); E, Case 5 (aged 47 yrs). Bars = 10 μ m.

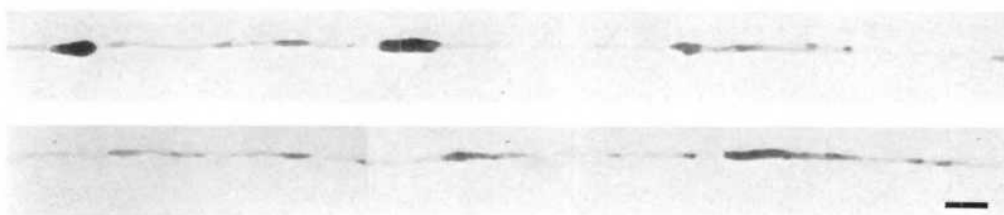


FIG. 2. *Case 3*. Teased fibre from sural nerve biopsy. Focal myelin thickenings, demyelinated segments and myelinated segments of varying length and thickness are present. There is a slight overlap in the two consecutive parts. Bar = 50 μ m.

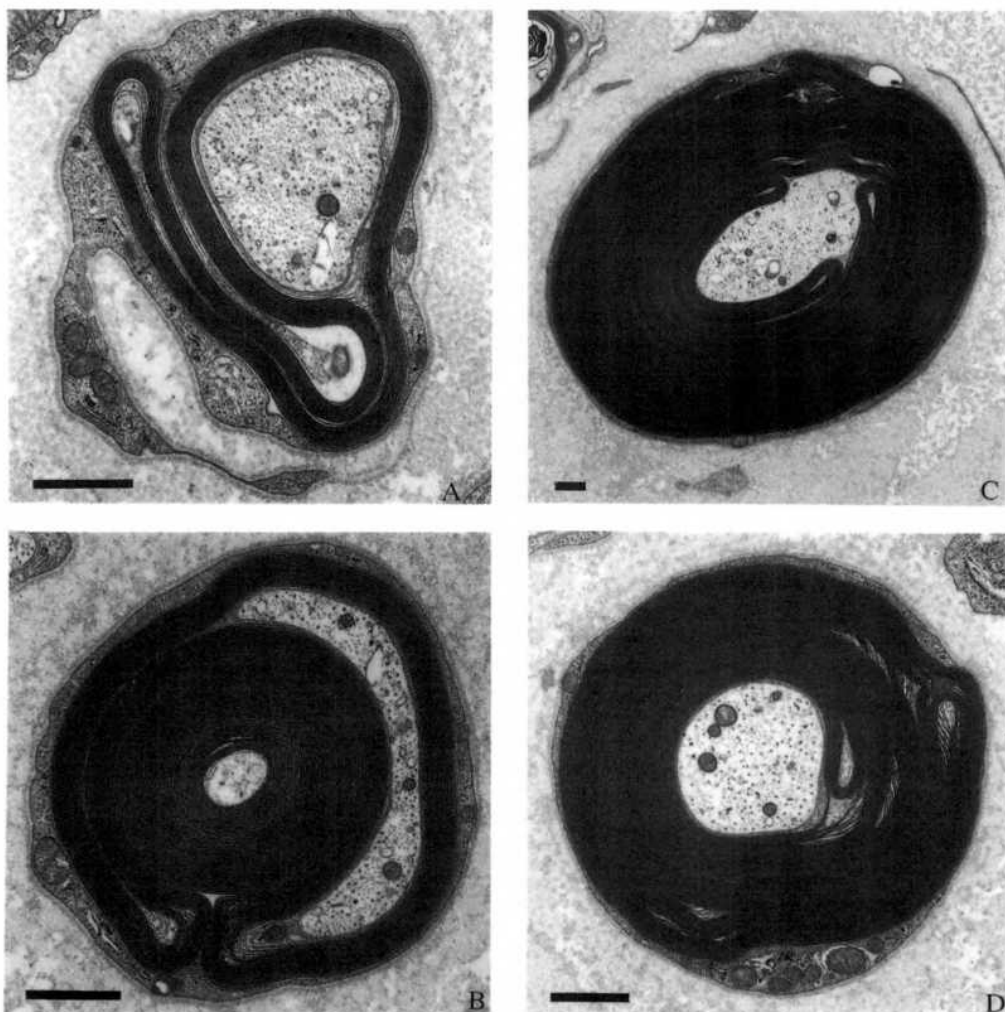


FIG. 3. Examples of hypermyelination on cross-section. A, stage of redundant loop formation (*Case 3*). B, external redundant loop, coiled up next to the axon (*Case 2*). C, external and internal redundant loops (*Case 1*). D, intramyelin folds (*Case 3*). Bars = 1 μ m.

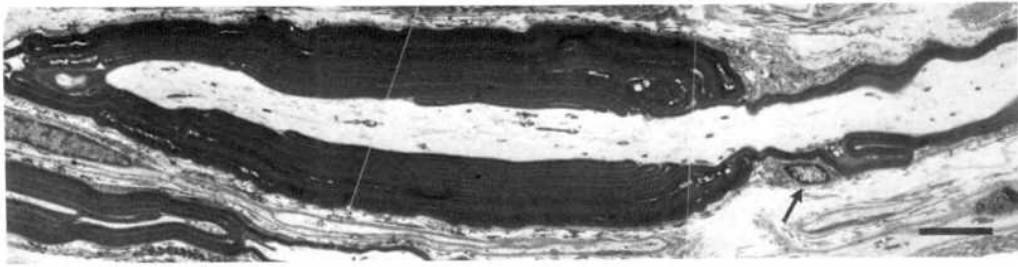


FIG. 4. *Case 1*. Complex myelin foldings on longitudinal section of tomacula. To the right of the Schwann cell nucleus (arrow) early loop formation is evident. Bar = 5 μ m.

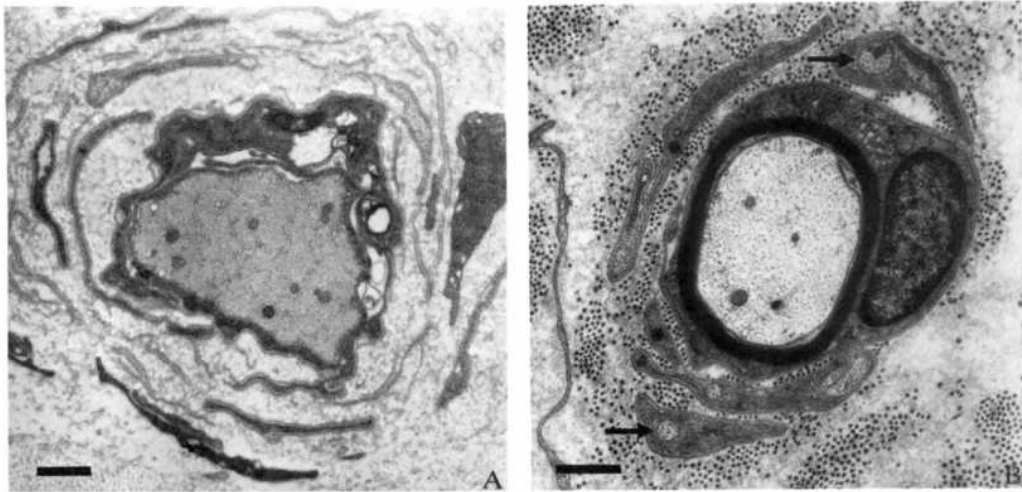


FIG. 5. Onion bulbs. A, *Case 2*. Thin Schwann cell lamellae are intermingled with double-layered basement membranes. Stage of demyelination. High densities of axon organelles. B, *Case 4a*. Small onion bulb composed of flattened Schwann cell processes surrounding a remyelinated fibre. Small unmyelinated axons are seen in the outer lamellae (arrow). Bars = 1 μ m.

thin Schwann cell processes and many double layered basement membranes, surrounding demyelinated (nonmyelinated) or thinly (re)myelinated axons (fig. 5A). In Cases 4a and 5, onion bulbs composed of concentric Schwann cell processes were rather frequent and sometimes large (fig. 5B). The onion bulbs were mostly denervated or surrounded the few remaining myelinated fibres. The outer lamellae of the onion bulbs occasionally contained unmyelinated axons.

Signs of active myelin breakdown were rare, but encountered in all patients. Demyelinated and some remyelinated axons often exhibited a high density of neurofilaments and microtubules (fig. 5A). Active axonal degeneration was not observed. Bands of Büngner were occasionally seen in the adults. Unmyelinated axons were normal, both in estimated number and appearance. Intra-axonal lamellated bodies as observed by Nordborg *et al.* (1984) were not encountered. There was a massive increase in collagen fibrils.

Morphometry

Morphometric data are listed in Table 4. All teased fibres showed demyelinated segments and nearly all showed focal myelin thickenings. About 50–75% of the internodes showed one or more of these tomacula. Only Case 4a had some fibres without tomacula, but in this case teased fibres, though isolated over 4–7 mm, often exhibited only one or two short myelinated segments, the remaining being demyelinated. The maximum diameter of the tomacula ranged from 24 to 14 μm in the 5 cases. Increase in total transverse fascicular area was mild. The density of the myelinated fibres was reduced. In the 2 infants, the reduction might be attributed merely to an increase in total transverse fascicular area, but in the 3 eldest patients a loss of myelinated fibres was present. This is obvious from the total number of myelinated fibres with normal values in the infants and a decrease with age in the other patients (fig. 6).

TABLE 4 MORPHOMETRY

	Case				
	1	2	3	4a	5
Teased fibres					
% with demyelinated segments	100	100	100	100	100
% with tomacula	96	100	98	72	100
Maximum diameter of tomacula (μm)	24	23	21	21	14
TTFA (mm^2)	1.10	0.97	0.80	1.35	0.58
Normal for age*	0.61	0.61	0.98	0.98	1.16
Density (number/ mm^2)					
Myelinated fibres	8740	8040	4480	710	240
Normal for age**	15 390	15 390	10 060	10 060	9760
Demyelinated fibres	2420	1580	670	480	200
g ratio (% >0.8)***	54	59	41	69	70

* Mean of age-matched controls: 2–6 yrs, $n = 4$; 11–30 yrs, $n = 5$; 31–50 yrs, $n = 3$. ** Mean of age-matched controls: 2–6 yrs, $n = 11$; 11–30 yrs, $n = 10$; 31–50 yrs, $n = 5$. *** Normal range: 0–3 yrs, 0.70–0.80; >10 yrs, small fibres 0.65–0.80, large fibres 0.55–0.65 (Jacobs and Love, 1985) TTFA = total transverse fascicular area.

Myelinated fibre histograms in all cases showed a unimodal pattern with an age-dependent loss of fibres, especially of the larger diameters. An axon histogram, however, gives a more reliable representation of the actual fibre loss per diameter group, because demyelinated axons are included, and on the other hand myelin thickening is ignored to avoid an overestimation of the larger diameter group. As shown in fig. 7, axons disappeared with increasing age, especially axons with diameters above 4 μm .

The g ratio was determined of all (presumed) myelinated fibres. Measurements through tomacula were included in this way, which makes, of course, a mean g ratio a misleading parameter. But the graphical representation of the g ratio of the single fibres per case gives a good illustration of both hypomyelination and tomacula formation (fig. 8). The g ratio ranged from 1 (axon diameter = fibre diameter, i.e., non or demyelinated fibres) to values below 0.2 (extremely thickened myelin sheaths). All axon diameters showed this large dispersion in g ratio. A considerable percentage of the fibres was hypomyelinated, i.e., with a g ratio above 0.80 (Jacobs and Love, 1985; Ouvrier *et*

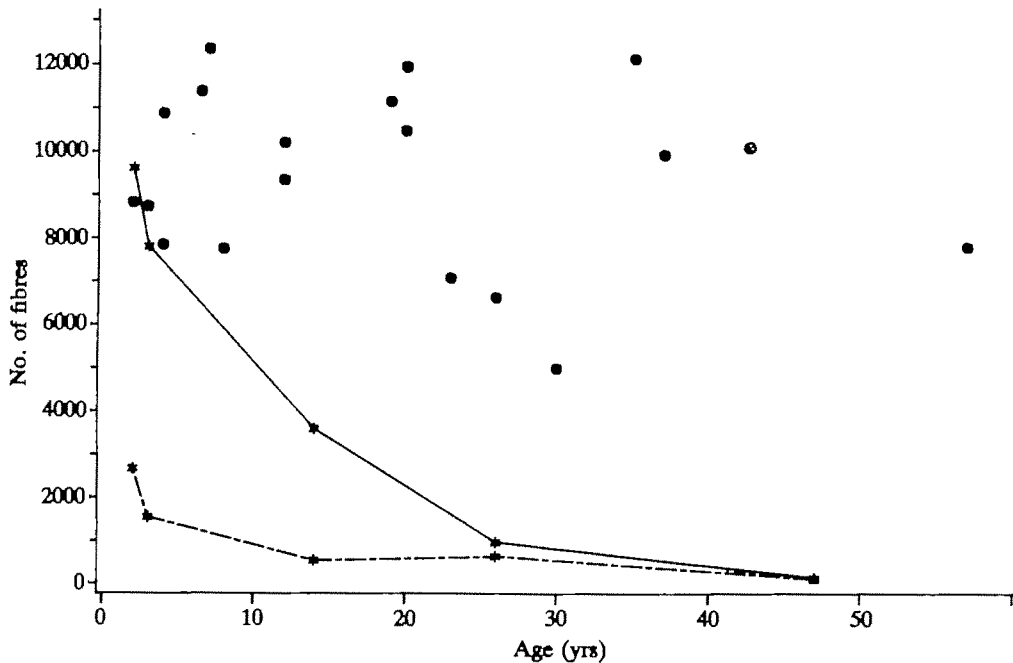


FIG. 6 Total number of myelinated fibres (continuous line) and demyelinated fibres (broken line) in the 5 index cases (*) compared with total myelinated fibre numbers in 19 controls of different age (●).

al., 1987) (Table 4). In the adults, fibres with a g ratio in the normal range (small fibres 0.65–0.80, large fibres 0.55–0.65; Jacobs and Love, 1985) were sparse; most fibres were non or demyelinated, but some showed abnormal thick myelin.

DISCUSSION

The 6 patients (5 index cases and 1 affected sib) described in this paper were suffering from a chronic progressive demyelinating neuropathy with congenital or early infantile onset. The disease progressed very slowly, most perceptibly until adolescence. In the adults a slight progression of the disease could be noticed only in retrospect over many years. Around puberty, all patients developed scoliosis. The severity of the disease differed markedly in 2 sibs. Case 4a became wheelchair dependent at age 12 yrs, whereas her brother is still ambulant at 38.

The occurrence of the disease in both sexes and in sibs (1 proven by clinical investigation and 1 probable by history) but not in the parents strongly suggests autosomal recessive inheritance.

Clinically, electrophysiologically and genetically our cases are compatible with HMSN type III (Dyck, 1975; Ouvrier *et al.*, 1987). CSF protein levels were not elevated in the infants. Although elevated CSF protein levels are usually considered part of the symptom complex of HMSN type III, several reports have mentioned normal values (Hagberg and Lyon, 1981; Guzzetta *et al.*, 1982).

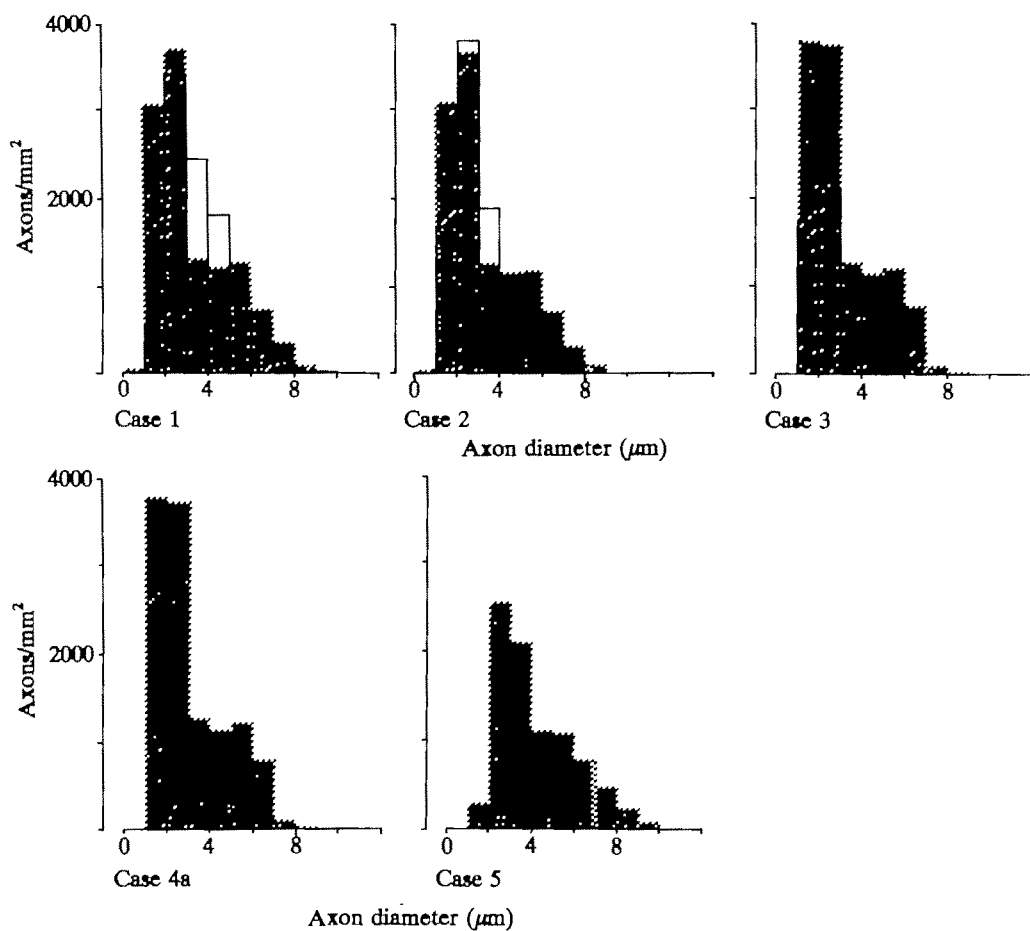


FIG. 7. Diameter histogram of axons belonging to the myelinated fibre category in the 5 index cases (white area) in comparison with age-matched control (hatched area).

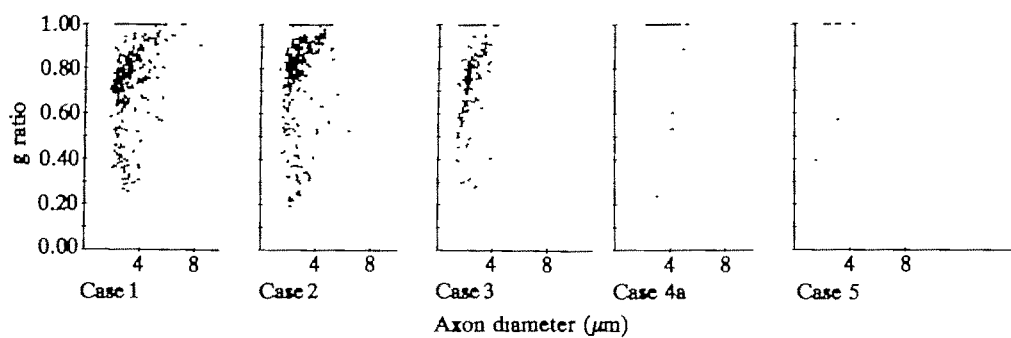


FIG. 8. Distribution of g ratios belonging to the myelinated fibre group, ranging from 1.00 (fibre diameter = axon diameter) to very low values (extremely thickened myelin sheaths).

A prominent percentage of the presumed myelinated fibres in our cases was hypomyelinated, that is, with a g ratio >0.80 (Jacobs and Love, 1985; Ouvrier *et al.*, 1987). But the most striking and discriminating feature from HMSN type III was the abundance of focal myelin thickenings present in nearly all teased fibres. Focal myelin thickening is a nonspecific feature and has been described in several clinically unrelated disorders. There are a few reports of the occurrence of focal myelin thickenings in congenital hypomyelination neuropathy (Nordborg *et al.*, 1984; Lütschg *et al.*, 1985; Vallat *et al.*, 1987; Vital *et al.*, 1987). Some of the published cases might be identical to ours but in most, lack of information about clinical features, electrophysiological findings, investigation of parents and/or frequency of tomacula precludes a critical comparison. Recently, Ohnishi *et al.* (1989) published 2 cases of a demyelinating motor and sensory neuropathy, probably of autosomal recessive inheritance, with excessive myelin outfoldings in sural nerve biopsy. In 1 case, symptoms started in childhood, in the second, onset was not until adult life. Morphologically the cases showed resemblances to ours, although the authors stressed the dissimilarities of the more irregular myelin outfoldings in their cases with respect to the more regular myelin formations of the tomacula in HLPP, as in our cases. From the published data it is obvious that focal myelin thickenings in sporadic or autosomal recessive segmental demyelinating neuropathy is not confined either to congenital or early infantile cases or to cases with a very markedly reduced conduction velocity.

Dayan *et al.* (1968) described focal myelin aberrations, called 'globules', in 2 cases with a progressive motor and sensory neuropathy, 1 certainly, the other possibly of autosomal dominant inheritance. Based on the clinical, genetic, electrophysiological and morphological data their cases might be classified as HMSN type I. Comparable alterations of the myelin sheaths in cases of dominantly inherited HMSN type I have been described in teased fibres or on ultrastructural examination by several authors (Dyck *et al.*, 1968, 1970; Madrid *et al.*, 1977; Low *et al.*, 1978; Van Wensen, 1980). Said (1976) examined sural nerve biopsies of a mother and a son from a family originally described by Roussy and Lévy (1926), and at present classified as HMSN type I (Yudell *et al.*, 1965). Said found in teased fibres numerous myelin thickenings next to demyelinated areas, imitating wallerian degeneration. A possible 'pseudo-wallerian' degeneration was also noted by Marie and Bertrand (1918) in dominantly inherited hypertrophic neuropathy (Said, 1976). These 2 reports might also be examples of the occurrence of focal myelin thickenings in cases of HMSN type I.

In hereditary liability to pressure palsies (HLPP), designated as tomaculous neuropathy by Madrid and Bradley (1975), large focal myelin thickenings are considered to be characteristic for the disorder (Behse *et al.*, 1972). HLPP is inherited as an autosomal dominant trait; some segmental de and remyelination and onion bulb formation are features of the affected nerves (Madrid and Bradley, 1975; Van Wensen, 1980; Meier and Moll, 1982). In our cases, the maximum size of tomacula falls into the lower range of HLPP tomacula (Van Wensen, 1980). The incidence of tomacula is higher than the incidence generally reported in HLPP (Behse *et al.*, 1972; Madrid and Bradley, 1975; Van Wensen, 1980). Clearly our cases do not fit to the clinical, genetic and electrophysiological criteria of HLPP (Meier and Moll, 1982).

Focal myelin thickening was also reported in some cases of IgM_k paraproteinaemia (Nardelli *et al.*, 1981; Vital *et al.*, 1985). The myelin thickenings showed the same

ultrastructural configurations as observed in tomaculous neuropathy (Vital *et al.*, 1985). Exposure of peripheral nervous system cultures to heated experimental allergic neuritis serum has likewise shown focal myelin thickening in addition to other myelin aberrations (Raine and Bornstein, 1979). In the 2 latter examples demyelination is of known primary origin.

Considering our cases as showing different phases of one disease, it is evident that the morphology of onion bulbs changes with age. The onion bulbs in the children were mostly small, and the Schwann cell whorls were frequently intermingled with many double-layered basement membranes. With increasing age onion bulbs became larger with abundant concentric layers of Schwann cell processes. Redundant basement membranes were seen infrequently (Case 4a) or were hardly present (Case 5). A similar phenomenon was noticed by others in cases of congenital motor and sensory neuropathy (Guzzetta *et al.*, 1982; Lütschg *et al.*, 1985). However, in our patients the onion bulbs were, although sometimes as large (Cases 4a, 5), not as ubiquitous as in classical HMSN type III (Dyck, 1975; Ouvrier *et al.*, 1987). In Case 5, onion bulb-like structures composed of many flattened Schwann cell processes dominated the picture. Well-developed onion bulbs with a central axon were seen infrequently. The occurrence of tomacula in 50–70% of the myelinated internodes of every teased fibre discriminates this case from HMSN type III. The total number of axons presumed to belong to the myelinated fibre population was still within normal ranges in the infants (fig. 6). This is in accordance with the findings of Guzzetta *et al.* (1982) in their cases of early infantile and childhood hypomyelinating neuropathy, corresponding to HMSN type III. In the 3 eldest patients axon loss became obvious (fig. 6). Axon loss is a common feature in demyelinating processes (Dyck *et al.*, 1984). It might be responsible for the increase of functional disability, as in HMSN type I (Roy *et al.*, 1989). Likewise, both the progression of disability and axonal loss in our patients were most obvious during childhood and puberty, both following a more steady course from adolescence onwards.

As observed by several authors (Dyck, 1975; Raine, 1977), many demyelinated axons and some remyelinated axons showed a high density of neurofilaments and microtubules suggestive of axonal atrophy (fig. 5A). Dyck (1984) considered this phenomenon as evidence for a primarily neuronal defect in HMSN type I. But axonal atrophy of demyelinated fibres is also seen in primarily demyelinating processes such as experimental allergic neuritis (Raine, 1977).

With respect to pathogenetic mechanisms, it is reasonable to assume that in our patients redundant loop formation and segmental demyelination are different aspects of the aetiological defect. Because in the 2 infants most tomacula were not surrounded by extra Schwann cell processes, it is obvious that the tomacula in our patients are not merely a consequence of segmental de and remyelination. Redundant myelin loops are occasionally seen in the early stages of normal myelinogenesis in human and animal fetal nerves (Dunn, 1970; Ochoa, 1971), but apparently disappear during maturation. In IgM_k paraproteinaemia a defect in Schwann cell-axon interaction can lead to focally folded myelin and segmental demyelination (Nardelli *et al.*, 1981; Vital *et al.*, 1985). In approximately 50% of cases of IgM paraproteinaemia with peripheral neuropathy antibodies directed against myelin-associated glycoprotein (MAG) are responsible for the demyelination process (Hays *et al.*, 1987). There is clear evidence that MAG plays a role in Schwann cell-axon interactions during myelinogenesis (Quarles, 1983/1984;

Martini and Schachner, 1986; McGinnis *et al.*, 1988). Studies in two types of hypomyelinating mutant mice also support the view that a disturbance in Schwann cell-axon interaction expressed by alterations in the normal immunocytochemical localization and biochemical composition of MAG can result in demyelinating disease (for review, see Quarles, 1983/1984). By analogy it could be supposed that in the present cases the processes of demyelination and focally folded myelin are both the consequence of a defect in or an alteration of factor(s) providing normal Schwann cell-axon interaction during myelin formation.

We conclude that the described cases represent a congenital motor and sensory neuropathy with chronic segmental demyelination, characterized by an abundance of redundant loop formation and only moderate onion bulb formation. The concomitant occurrence of focally folded myelin and segmental demyelination in these patients is, by analogy with cases of known pathogenesis, suggestive of a defect in myelinogenesis, probably initiated by a defect in Schwann cell-axon interaction. These cases corroborate the great heterogeneity of congenital motor and sensory neuropathies.

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SYMPTOMATIC AND ESSENTIAL RHYTHMIC PALATAL MYOCLONUS

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SUMMARY

Rhythmic palatal myoclonus (RPM) is a rare movement disorder consisting of continuous synchronous jerks of the soft palate, muscles innervated by other cranial nerves and, rarely, trunk and limb muscles. It usually develops secondary to brainstem or cerebellar disease (symptomatic RPM). Some patients, however, fail to show evidence of a structural lesion (essential RPM). A total of 287 cases with RPM from the literature including 210 cases with symptomatic and 77 cases with essential RPM have been reviewed and analysed statistically to look for criteria separating the two conditions. Patients with essential RPM usually have objective earclicks as their typical complaint which is rare in the symptomatic form. Eye and extremity muscles are never involved. The jerk frequency is lower in essential than in symptomatic RPM. Patients with essential RPM are younger and have a balanced sex distribution as compared with a male preponderance in the symptomatic form. The rhythmicity of RPM seems to be more profoundly influenced by sleep, coma and general anaesthesia in essential than in symptomatic RPM. We conclude from these results that essential RPM should be separated as a distinct clinical entity. Symptomatic RPM is a rhythmic movement disorder whose pathogenesis is quite well established. The cells of the hypertrophied inferior olives are believed to represent the oscillator. Among other possibilities, essential RPM may represent its functional analogue, based on transmitter changes only. Such a relationship could be of theoretical interest for the understanding of rhythmic hyperkinesias in general.

INTRODUCTION

Rhythmic palatal myoclonus (RPM) is a rare movement disorder characterized by rhythmic jerky movements of the soft palate and sometimes other brainstem-innervated muscles. Occasionally, the limbs may be affected by a postural tremor synchronized to the jerks of RPM. Most reports since those of the last century (Boeck, 1867; Spencer, 1886) have described single cases and different terms such as palatal tremor, palatal nystagmus, palatal myoclonus and brainstem myorhythmia have been proposed. Although there are many objections against the term 'rhythmic palatal myoclonus' (Deuschl *et al.*, 1986), we apply this term as it has been generally used during the last 20 years in the Anglo-American literature (*see* Addendum). The clinical significance of this disorder is limited not only because it is rare but also because many of the patients have no complaints related to RPM. However, if at least one of the cardinal subjective complaints such as postural tremor, oscillopsia or persistent earclicks is present, the patients can be severely inconvenienced.

Compared with other movement disorders the pathology of this hyperkinesia is rather well established due to the pioneering work of Klien (1907), Guillain and Mollaret (1931),

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Lapresle and Ben Hamida (1965, 1968) and others. Nowadays it is regarded as the prototype of a hyperkinetic movement disorder depending on a central pacemaker (Schenck, 1965; Llinás, 1984), chiefly because the rhythmic jerks are time-locked in different muscles. Moreover, it is believed that it could serve as a model for other rhythmic hyperkinesias such as tremor (Llinás, 1984). The inferior olive is considered to be the pacemaker (Trelles, 1968). Three observations support this view. First, in autopsied cases with RPM there is a 'hypertrophic degeneration' of the cells of the inferior olive, with enlargement of the cell bodies, fibrillary gliosis, and gross hypertrophy of the whole of these structures (Gautier and Blackwood, 1961; Aberfeld, 1966; Koeppen *et al.*, 1980b; Lapresle, 1986). Secondly, even the normal inferior olive cells have the capacity for spontaneous synchronized rhythmic discharges, as suggested by animal experiments (Llinás, 1984; Llinás and Yarom, 1986; Llinás and Mühlethaler, 1988). Thirdly, there is recent evidence from positron emission tomography that the inferior olive is hyperactive in patients with RPM as shown by increased glucose uptake (Dubinsky and Hallett, 1988), probably reflecting the continuous rhythmic overuse of these cells. The hypertrophic cells of the inferior olive are thereby regarded to represent the pacemaker for the hyperkinesia. There is much evidence obtained by careful pathoanatomical observations that this unique alteration of the inferior olive develops secondary to a lesion within a pathway from the contralateral dentate nucleus via the brachium conjunctivum and the ipsilateral central tegmental tract to the inferior olive (Lapresle and Ben Hamida, 1965, 1968), originally referred to as the Guillain-Mollaret triangle. In clinical terms most of the patients with RPM have a clearcut history of cerebellar or brainstem disease and many of them have neurological symptoms or clinical findings which confirm this localization.

Since the earliest reports of RPM, however, there were cases in which there was no indication of any such focal lesion. Recent papers classify these cases as 'idiopathic' RPM (Lapresle, 1979; Dubinsky and Hallett, 1988). The hypothesis advanced in the present paper is that they represent a distinct movement disorder. The goal of our study was to search for criteria that may help in separating the two conditions, that is, to look for distinguishing features between symptomatic and idiopathic cases. This approach is difficult as only few neurologists throughout the world have seen personally more than 10 patients, which is underlined by the fact that up to now mostly single cases have been published (for review, *see* Schenck, 1965). Hence it is impossible to answer the above question on the basis of personally examined patients. We therefore evaluated case histories from the literature since 1867 in which the descriptions were adequate and fulfilled certain criteria to be discussed below. The data were analysed statistically. They are consistent with the hypothesis that cases with idiopathic RPM should be separated as a distinct condition. For this disease we propose the term 'essential rhythmic palatal myoclonus', as the adjective 'essential' is commonly used for diseases with a clearly defined clinical picture whose aetiology and/or pathophysiology is unknown (*see* Addendum).

MATERIAL AND METHODS

A total of 287 cases from 171 publications have been evaluated according to a check list of 18 items (*see* Appendix 1). Only cases published in German, English, French, Italian or Spanish have been taken

into account. Not all individual case reports included all the desired information. Hence for some items the number of items of available data is below 287. For several symptoms the data have been analysed according to the different aetiologies within symptomatic RPM; for others this was not possible because of limited information. Nevertheless, rare symptoms or observations have also been included if they were of special clinical interest.

With this approach several factors might affect the reliability of our investigation. Some of the data such as sex and age are highly reliable, whereas others such as disease duration or details of the neurological examination might be biased. Hence many items had to be restricted to cases whose clinical state has been described in detail. The selection criteria for each item are, in general, explained in the appropriate section of Results. However, some of them deserve special comment.

Inclusion criteria and definitions

Two criteria had to be fulfilled for a case to be included in the present study. The first was the description of rhythmic myoclonic movements of the soft palate, even if thereby one of the most famous case reports (Spencer, 1886) had to be excluded. The second criterion was the presence of sufficient information to classify the aetiology of the disease according to the criteria discussed below. Concerning the latter question it was especially noted whether RPM had an underlying neurological disease or not.

Aetiological classification

All patients have been classified in one of the following two groups. They have been assigned to *symptomatic RPM* if they had (1) an organic disease of CNS or cranial nerves; (2) and/or a residual lesion of the CNS; (3) and/or any abnormalities on neurological examination other than RPM; (4) and/or a medical history of any of items (1)–(3) in the past.

Several groups of symptomatic RPM were separated, such as cerebrovascular disease, degenerative diseases, encephalitis, multiple sclerosis, tumours, trauma, and 'other symptomatic aetiologies'. Cases with defined diseases such as syringobulbia were classified in the latter group if not more than 4 of these cases had been found in the literature. Moreover, those cases have been included in this group for which no firm diagnosis could be achieved but in which the clinical history probably indicated an earlier neurological disease or in which there were abnormalities other than RPM on neurological examination.

Within the *essential RPM* group all patients were included where the medical history, the subjective complaints and the neurological examination gave no hint of any related neurological disease. These criteria have been applied very strictly as even the weakest signs for a neurological abnormality other than RPM resulted in classification among 'other symptomatic aetiologies'. Therefore the possibility cannot be excluded that some cases are included among 'other symptomatic aetiologies' who had essential RPM together with another accompanying unrelated disease. However, this possible bias had to be accepted to avoid any false positive classifications in the group with essential RPM which is in the focus of the present report.

Rating of involved muscles

In the case reports, the involvement of additional muscles or muscle groups in the rhythmic RPM activity is based on clinical investigation only. The general criterion for the involvement of a muscle in the hyperkinesia is that it showed jerks synchronous with those in the soft palate. For some cranial nerve muscles it is easy to decide whether they are involved; for others it is very difficult. Based on our own clinical experience we decided to collect the data in terms of specific muscles, topographical regions or even clinical symptoms. The following criteria have been applied for separating muscles or regions.

Eye: involvement of external ocular muscles has been accepted if time-locked nystagmus of one or both eyes was described. *Click*: objective clicking sounds. This reflects the activation of the tensor veli palatini, the eustachian tube or the middle ear muscles (see Discussion; Zöllner, 1942; Pulec and Simonton, 1961; Slack *et al.*, 1986). *Upper face*: innervation zone of the upper branches of the facial nerve including those to the nose. *Lower face*: innervation zone of the lower branches of the facial nerve including the perioral region, chin and platysma. *Tongue*: involvement of the tongue. *Soft palate*: involvement of the soft palate regardless of the direction of movement. *Pharynx*: involvement of the visible pharynx (inspection with mouth open). *Inner larynx*: involvement of the vocal cords (ascertained by laryngoscopy). *Floor of the mouth*: contraction of the inframandibular region, except platysma. *Outer larynx*: movements of the larynx seen by inspection or external palpation. *Trigeminal nerve muscles*: masseter or temporal muscles. *Accessory nerve muscles*: trapezius or sternocleidomastoid muscles (partially overlapping with head tremor). *Axial*

muscles: muscles of the trunk, intercostal muscle and diaphragm. *Upper limbs*: postural tremor of the upper extremities. *Lower limbs*: postural tremor of the lower extremities. *Head tremor*: tremor of the head (overlapping with accessory nerve muscles).

Statistical analysis

The total data were subjected to statistical analysis (BMDP). χ^2 analysis, the Wilcoxon test and the t test were also applied.

RESULTS

Epidemiological data

Aetiology

A total of 287 cases could be ascribed either to symptomatic or essential RPM according to the criteria given in Methods. The majority of cases were easily classifiable and mostly the author's diagnosis of the specific cause was accepted. The group with symptomatic aetiologies could be subdivided into several subgroups.

There were 210 patients with symptomatic RPM (*see* fig. 1). Of these, 115 had cerebrovascular disease including 5 cases of syphilitic vasculitis. Seven patients had degenerative diseases, 5 encephalitis, 9 multiple sclerosis, 19 tumours and 23 brain trauma; 32 were classified among other aetiologies (for the classification of each case, *see* Appendix 2).

There were 77 patients with essential RPM according to our definition. Mostly the aetiology of these cases was stated to be unknown by the authors. Particularly in the older literature, a number of speculations as to the underlying cause or diagnosis were proposed such as common colds, otitis media in the contralateral ear or inflammatory disorders in the nasopharynx, minor head trauma, a neurasthenic disposition or hysteria, tics, etc. These diagnostic hypotheses are believed to be unrelated to RPM and were not taken into account.

Also included were 41 cases which fulfilled all our criteria for essential RPM except that the neurological examination was not reported in detail. These were mostly cases from the otolaryngological literature. This group, however, has been tested statistically

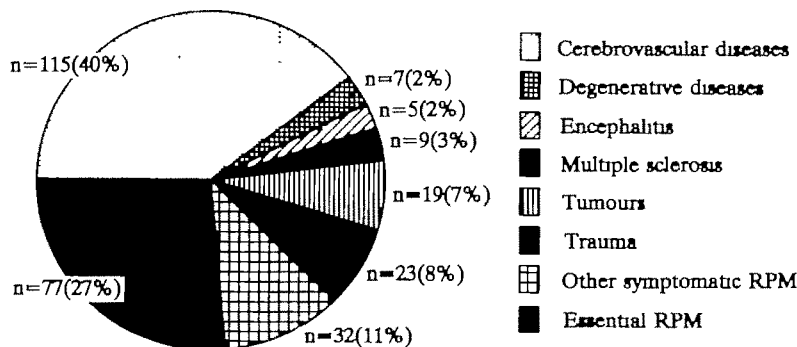


FIG. 1 Aetiology of 287 cases with RPM. Note that more than a quarter belong to essential RPM.

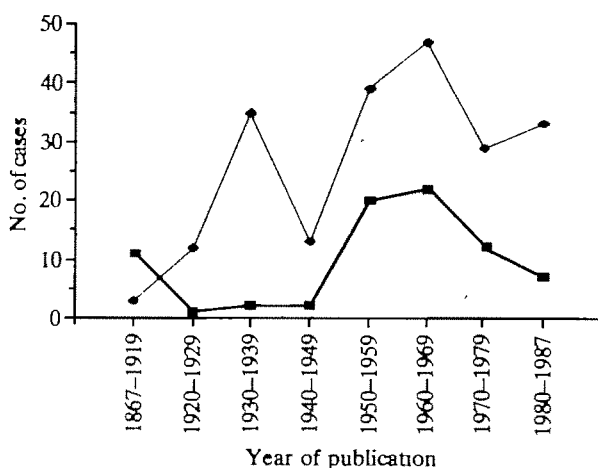


FIG. 2 Distribution of 287 cases with symptomatic and essential RPM according to the year of publication. Diamonds = symptomatic RPM (n = 210), squares = essential RPM (n = 77).

in all respects reported here with χ^2 test against the remaining 36 cases of the group 'essential RPM'. No significant differences were found concerning all the items reported below.

Year of publication of the cases

It is of interest to establish whether the cases with essential RPM were observed only during a limited period of the sampling time of our study. That this is not so is evident from fig. 2 which shows the number of cases in both groups related to their date of publication. Even among the earliest descriptions there are cases fitting with our definition of essential RPM. Between 1920 and 1950 the literature was dominated by French publications which focused on symptomatic RPM. During that period only a few cases with essential RPM were published.

Age distribution

Data as to the age of the subjects were available in 283 cases. These give the age at the time of examination of each case. RPM is a syndrome occurring in all age groups. The youngest was an 18-month-old girl who developed RPM after an episode of fever and diarrhoea (Sridharan, 1983). She was classified among 'other symptomatic aetiologies' as CNS involvement was not excluded. The oldest patient was a 91-yr-old man suffering from a stroke (Rao and Kataria, 1969). The mean age in the groups with symptomatic RPM was 49.2 ± 16.7 (mean $\pm$ SD) and in the group with essential RPM it was 30.4 ± 14.9 yrs. The difference is significant ($P < 0.001$, Wilcoxon test). Symptomatic RPM has a peak in the age distribution between 50 and 60 yrs and essential RPM between 30 and 40 yrs. If the different aetiologies for symptomatic RPM are separated, the groups with cerebrovascular disease, degenerative diseases, encephalitis, inflammatory diseases and tumours coincide with the combined distribution, whereas those with RPM following head trauma or 'other symptomatic aetiologies' are younger with a peak at a lower age (30-40 yrs).

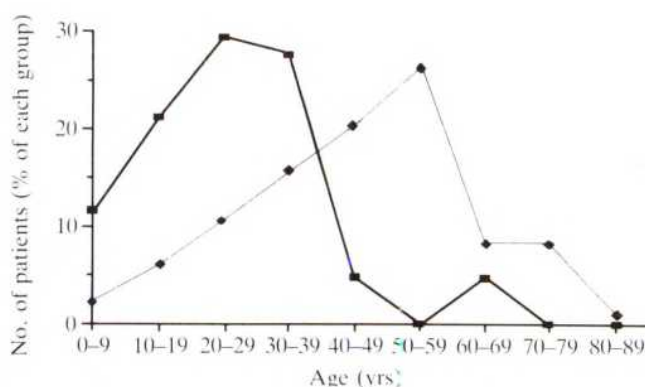


FIG. 3. Age at presumed onset of the disease in 144 patients. Note that cases of RPM with onset after the age of 40 yrs are rare. Diamonds = symptomatic RPM ($n = 83$); squares = essential RPM ($n = 61$).

In a total of 144 cases reliable data could be obtained on the respective duration of the disease (*see* section on natural course of the hyperkinesia). If the duration of RPM is subtracted from the age at description, the age at onset is obtained. The mean values were 45.1 ± 17.3 yrs for symptomatic and 24.8 ± 12.9 years for essential RPM. Fig. 3 shows these data. It is evident that essential RPM begins only rarely after the age of 40 yrs. Among the cases with symptomatic RPM, those with a presumed traumatic cause are overrepresented as they were under continuous observation and therefore frequently had a precise onset.

It is concluded that patients with essential are younger than those with symptomatic RPM except for those with head trauma or 'other symptomatic aetiologies'. This was found for the age at examination as well as for the presumed age at onset.

Sex distribution

Data as to the sex of the patients reported here were available in 284 cases. Some diseases are known to occur predominantly in either males or females. Among the diseases that can cause RPM this applies particularly to cerebrovascular disease and head injuries where there is a male predominance, whereas brain tumours, for example, have a balanced sex distribution. On the whole, the 208 patients with symptomatic RPM (fig. 4) have a male preponderance (66%:34%). This general trend is seen in the majority of symptomatic cases except in the subgroups with degenerative diseases, encephalitis, MS and tumours which had a relation of about 1:1 between men and women. By contrast, the 76 cases with essential RPM have an approximately equal sex distribution (48%:52%). This difference between symptomatic and essential RPM is significant (χ^2 test, $P < 0.01$).

Medical history

Presenting complaints

For the clinical diagnosis it is important that the presenting complaints are quite different for patients with symptomatic and essential RPM (fig. 5). The presenting complaint

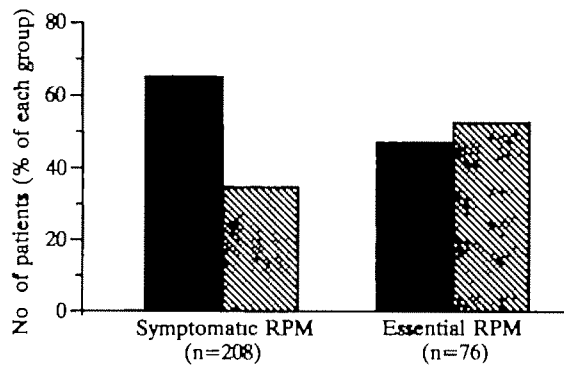


FIG 4. Sex distribution of 284 cases with symptomatic and essential RPM. Filled columns = male, hatched columns = female

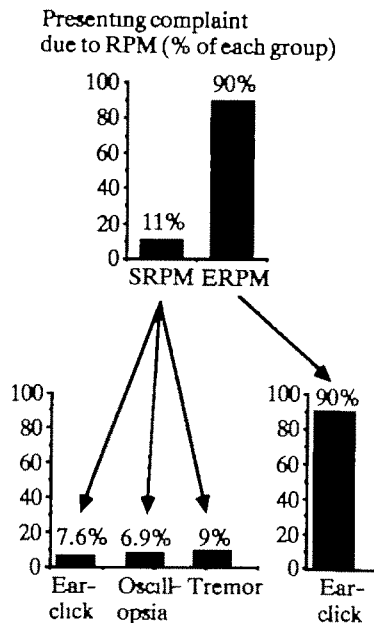


FIG 5. Presenting complaints of 192 patients with symptomatic RPM (SRPM) and 77 cases with essential RPM (ERPM).

was assessed for its relationship to the RPM itself (in case of earclicks, oscillopsia or postural tremor), to the underlying neurological disorder (e.g., brainstem stroke) or to be unrelated to both (detection by chance). Of the 192 cases with symptomatic RPM, only 21 (11%) presented with complaints caused by the RPM. These were 16 (8%) with earclicks, 14 (7%) with oscillopsia and 19 (10%) with tremor. The others had complaints related to the neurological disease underlying the RPM (158 patients, 82%) or they had been detected by chance (13 patients, 7%).

By contrast, 64 of the 71 cases (90%) with essential RPM had audible earclicks but never oscillopsia or tremor as their presenting complaint. The remaining 7 patients (10%) were detected by chance. The complaint of continuing audible earclicks seems to be a hallmark of essential RPM and is rare in symptomatic RPM.

Natural course of the hyperkinesia

It is generally assumed that RPM persists for life once established (*see* Schenck, 1965; Lapresle, 1979). Whether this is true for both symptomatic and essential RPM is of interest but can be answered only to a limited extent on the basis of the present data.

The first question was whether the duration of the disease differs between the groups. Only those cases have been taken into account for which firm data as to the onset of RPM were available. This was either the reported onset of a typical symptom (e.g., earclick) or an earlier detection of RPM on neurological investigation. In symptomatic RPM ($n = 86$ cases) the reported durations ranged between 2 days and 30 yrs (fig. 6) with a mean of 3.5 yrs. In essential RPM ($n = 61$ cases) the duration was estimated as between 1 month and 32 yrs with a mean of 4 yrs. Statistical tests revealed no significant differences. These data underline the fact that symptomatic and essential RPM are both longstanding and probably lifelong diseases.

Secondly, we looked for cases which had been observed until death. This was reported only in cases with symptomatic RPM and never for patients with essential RPM (*see* section on Modulation of RPM). Thirdly, we looked for cases with disease remissions. At least 3 patients with essential RPM were reported to have lost the disorder without relapses (Schenck, 1965; Ritter, 1973; Litman and Hausman, 1982). No convincing remissions in symptomatic RPM have been described. Two patients with RPM-like movements during encephalitis have been published (Carmon *et al.*, 1963), whose hyperkinesia disappeared after 6 wks with recovery of the encephalitis.

Finally, we looked for cases initially presenting with the clinical picture of essential RPM which later developed an underlying organic disease. One case was found in which RPM was the initial and isolated symptom of a slowly growing brainstem glioma (Guillain

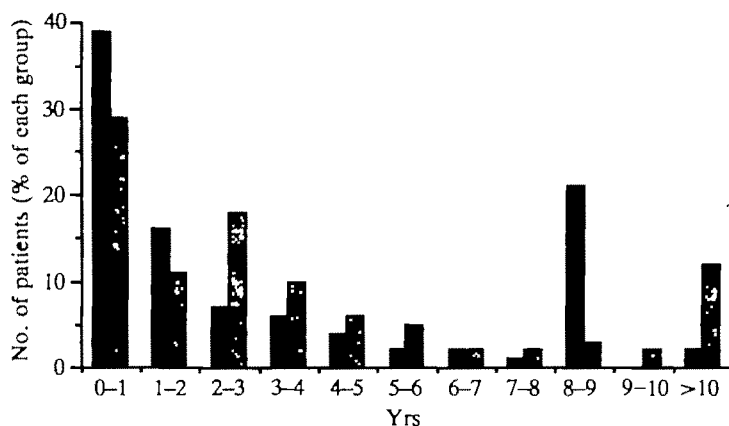


FIG. 6. Duration of RPM for 169 cases with symptomatic and essential RPM. Filled columns = symptomatic RPM ($n = 107$); hatched columns = essential RPM ($n = 62$).

and Mollaret, 1931; Case 1). However, as expected, the patient developed further neurological signs within half a year. It is concluded that essential RPM should be diagnosed only after an appropriate observation period. On the other hand, the long duration of the majority of cases with essential RPM makes it unlikely that they later developed a CNS disease manifesting by other symptoms than RPM alone.

Clinical investigation

Muscle groups involved

One of the hallmarks of RPM is the inclusion of various other brainstem or limb muscles in the synchronous jerks of the rhythmic hyperkinesia. If the eye muscles are involved, pendular nystagmus usually occurs and if the extremity muscles are implicated it usually takes the form of a reciprocal alternating postural tremor in antagonists, time-locked to the palatal movements.

With respect to the proposed distinction between symptomatic and essential RPM, it is of interest as to whether the territory of involved muscles is different in both groups. Fig. 7 displays these data (for rating criteria, *see* Methods). According to our selection criteria, the soft palate is involved in all cases. In patients with symptomatic RPM, the pharynx is often also visibly involved in the hyperkinesia. The next most frequent manifestation is involvement of lower facial muscles, usually of the chin or periorally. The remaining muscles are less frequently involved except the eye muscles. These often show a pendular nystagmus. However, only a few of these patients have oscillopsia. Striking differences were found when comparing symptomatic with essential RPM (fig. 7). In essential RPM mostly earclick is present, whereas trigeminal, accessory, limb

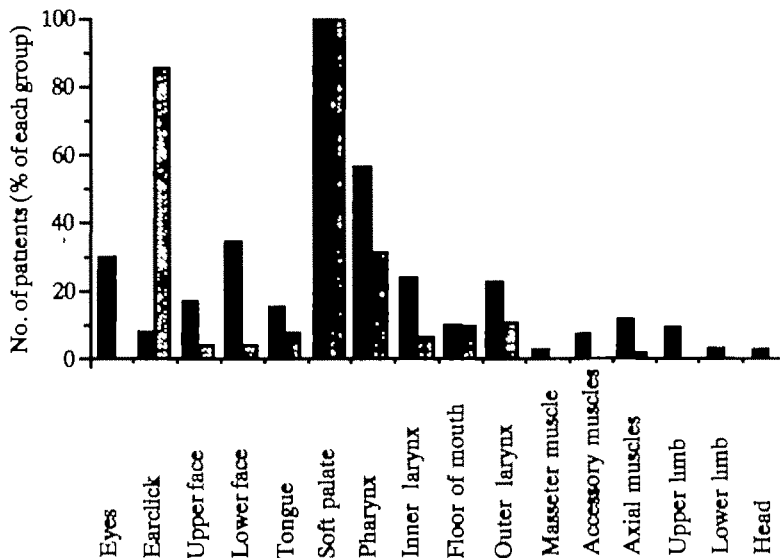


FIG 7. Muscles involved in 287 cases with RPM. For rating criteria, *see* Methods. Filled columns = symptomatic RPM (n = 210); hatched columns = essential RPM (n = 77)

or eye muscles are never involved. The difference between symptomatic and essential RPM is significant for earclicks ($P < 0.001$). The involvement of muscles causing audible earclicks, as well as the lack of involvement of eye, trigeminal and limb muscles, thus seems to be another hallmark separating essential from symptomatic RPM.

Laterality of RPM

The fact that RPM may be restricted to the cranial nerves on one side was recognized in the very early case reports. We have classified a case as unilateral if all the muscles that contributed were confined to one side. Even if a single muscle was affected contralateral to the more affected side, the case was rated as being bilateral. Accordingly, 59 of the 287 cases (20%) had unilateral and 228 had bilateral RPM. There were no significant differences between the symptomatic and essential RPM groups or between the different subgroups of symptomatic RPM. Hence this criterion does not separate symptomatic and essential RPM.

Frequency of the muscle jerks

Fig. 8 shows the frequency distribution of the muscle jerks in a single case as reflected in the interspike intervals. The mean is fairly close to the frequency per min as determined by visual inspection which in this particular case was 96–100/min, rated by 3 different observers. Simple counting of the jerks, undertaken since the earliest descriptions of RPM, therefore appears to be quite a reliable measure of the mean frequency.

Mean frequency data were available for 219 cases. Fig. 9 displays these, separated into symptomatic and essential cases. Symptomatic RPM cases have a mean frequency that is usually between 100 and 179 jerks/min with a peak at 120–139 jerks/min. Higher and lower frequencies are rare. When separating the data according to the different aetiologies the different subgroups have approximately the same distribution except those with traumatic RPM which includes a considerable number of cases with frequencies between 160 and 199 jerks/min.

The most striking feature is the difference between essential RPM and symptomatic RPM (fig. 9). The patients of the former group have significantly lower frequencies ($P < 0.001$, *t* test) and a much broader frequency distribution. In general, frequencies below 120 jerks/min are seen more often in cases with essential RPM, whereas those above 120 jerks/min are more common in symptomatic RPM.

Modulation of RPM

It has been emphasized frequently that one of the characteristics of RPM is its high resistance to many influences such as medication, sleep, and even general anaesthesia and coma (Schenck, 1965; Rondot and Ben Hamida, 1968; Lapresle, 1979, 1986). In a considerable number of cases the effect of one or other of these connections has been observed and we assessed whether some properties that reflect the capacity of modulation are equally distributed among cases with symptomatic and essential RPM.

Observation of RPM during coma

In a total of 13 cases of the present series the hyperkinesia was observed even up to the time of death in patients who were in coma (Klien, 1907 (2 cases); Grill and Lauren, 1932; Bender *et al.*, 1952 (2 cases); Nathanson, 1956 (3 cases); Bojinov and

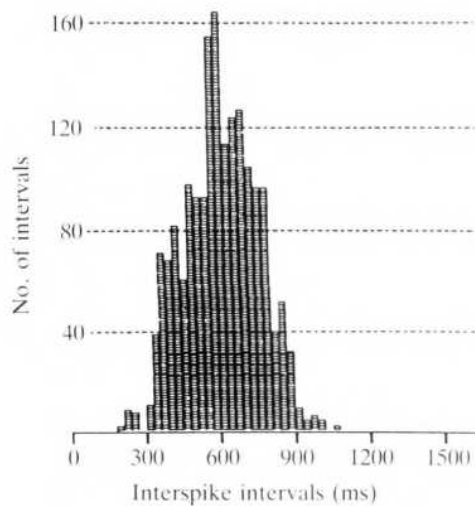


FIG. 8. Histogram of the interspike intervals of the myographically recorded perioral jerks in a case with symptomatic RPM (Deuschl *et al.*, 1986, Case 2). The mean value of this distribution is 614 ms corresponding to a frequency of 97 jerks/min. When the frequency was counted by visual inspection, nearly the same mean frequency was obtained. Bin width = 40 ms, 1800 interspike intervals.

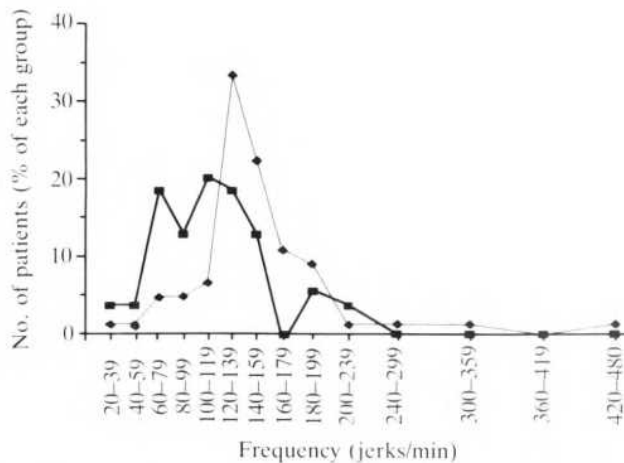


FIG. 9. Distribution of mean frequencies in 219 cases with RPM. Diamonds = symptomatic RPM ($n = 165$); squares = essential RPM ($n = 54$).

Lolova, 1968; Mastaglia, 1974; Jacobs and Bender, 1976; Turazzi *et al.*, 1977). All patients belong to the group with symptomatic RPM. Not a single case with essential RPM has been observed when in coma or terminally. Hence it is not known whether this criterion separates both types of RPM. On the other hand, the uniformity of this result in 13 cases is a strong argument that symptomatic RPM is not dependent on highly organized cortical functions.

Observations on RPM during narcosis

The effect of general anaesthesia with barbiturates on RPM was reported in 8 cases. Four had symptomatic RPM (Bender *et al.*, 1952; Dereux *et al.*, 1966; Nathanson, 1956 (2 cases)). All these patients had persisting RPM during narcosis. Two cases with essential RPM have been observed during barbiturate narcosis (Fatin, 1953; Götze, 1957), 1 during nitrous oxide narcosis (Cancura, 1969) and another during unspecified general anaesthesia (Kwee and Struben, 1972). In these 4 cases the RPM disappeared.

Observations of RPM during sleep

The movements of the soft palate are mostly reported to persist during sleep as far as can be ascertained by means of clinical inspection alone (Schenck, 1965; Lapresle, 1986). Only the pendular nystagmus related to RPM regularly disappeared during sleep (Chokroverty and Barron, 1969; Lynn, 1973; Nakada and Kwee, 1986).

Clinical observation on the hyperkinesia during sleep has been reported in 41 cases of the present series. Of 31 cases with symptomatic RPM, 29 (94%) had persistent RPM during sleep and in 2 it disappeared. In 10 patients with essential RPM the hyperkinesia was observed during sleep. Five of them had persistent RPM and in the other 5 it disappeared. In 16 of these 41 patients polygraphic sleep recordings were performed; Submental or perioral EMG electrodes were used for recording the hyperkinesia which might well not detect activity in the soft palate. Twelve patients with symptomatic RPM have been investigated and 10 of them showed persistent hyperkinesia (Chokroverty and Barron, 1969 (4 cases); Michel *et al.*, 1972; Lynn, 1973 (3 cases); Jacobs and Bender, 1976; Kaye *et al.*, 1982) but in 2 patients it stopped at least at stage 4 sleep or during REM sleep (Jacobs *et al.*, 1981; Montagna *et al.*, 1983). Four patients with essential RPM have been investigated. Two of them had persistent RPM during sleep (Kaye *et al.*, 1983 (2 cases)) and in 2 of them the RPM ceased (Meier-Ewert *et al.*, 1970; Lynn, 1973).

We conclude that, on the whole, symptomatic RPM is more resistant to sleep, coma or barbiturate anaesthesia than essential RPM, although a sufficient number of polygraphic recordings is still lacking.

Attempts at therapy

Many attempts have been made to improve the symptoms of RPM (Stern, 1949; Bender *et al.*, 1952; Bergman *et al.*, 1953; Nathanson, 1956; Hughes, 1965; Laskiewicz, 1966; Ekbom and Kukelberg, 1967; Tateishi, 1968; Chokroverty and Barron, 1969; Mastaglia *et al.*, 1974; Rhee *et al.*, 1974; Parnes, 1977; Magnussen *et al.*, 1977; Turazzi *et al.*, 1977; Williams *et al.*, 1978; Rahko and Häkkinen, 1979; Gauthier *et al.*, 1981; Sakai *et al.*, 1981; Jabbari and Gunderson, 1983; FitzGerald, 1984; Soso *et al.*, 1984; Ovelacq *et al.*, 1987).

Phenytoin, barbiturates, different benzodiazepines, 5-hydroxytryptophan and anticholinergic drugs (trihexyphenidyl) have been administered in single case studies which are partly well-controlled. Double-blind studies are not available. Successful treatment was achieved in 8 of 35 patients with symptomatic RPM and in 10 of 14 patients with essential RPM (*see* Table 1). Nevertheless, many other papers have reported that any therapy for RPM is only rarely successful.

Statistical analysis of the data concerning therapy is not possible; however, there is

TABLE 1. MEDICAL THERAPY OF RPM*

	<i>Symptomatic RPM</i>	<i>Essential RPM</i>
Phenytoin	0/6	2/3
Barbiturates	0/18	1/2
Benzodiazepines		
Diazepam	0/1	2/2
Clonazepam	2/2	0/0
Carbamazepin	2/4	2/4
5-HTP	2/2	1/1
Trihexyphenidyl	2/2	2/2

* No. of successfully treated patients/no. of tested patients.

an impression that essential RPM can be more successfully treated than the symptomatic form. Surgical techniques have been applied to cure the distressing earclicks. Tamponade of the eustachian tube (Zöllner, 1942) and perforation of the tympanic membrane (Kwee and Struben, 1972) were unsuccessful. At least partial relief from the earclick was reported following cutting the levator palatini muscle (Cancura, 1969) and the tensor veli palatini (Yajin *et al.*, 1985), or inspection of the posterior fossa with microsurgical techniques (Soso *et al.*, 1984). In conclusion, there is no commonly successful medical or surgical treatment for the subjective complaints in RPM; however, it is justified from earlier experience to test several substances. The effect of different therapies does not separate symptomatic and essential RPM.

Pathoanatomical findings of RPM

The hypertrophic degeneration of the inferior olive is regarded as a nearly constant finding (*see* Lapresle, 1986). The typical hypertrophic degeneration was found in 39 of the 46 cases with brainstem histology included in the present study. In 4, it was not mentioned (Herrmann and Brown, 1967; Bojinov and Lolova, 1968; Koeppen *et al.*, 1980a). There was definitely no hypertrophic but atrophic degeneration in 2 (Rao and Kataria, 1969; Masucci *et al.*, 1984 (1 case)) and a normal inferior olive in 1 case (Masucci *et al.*, 1984). However, all patients, including those without olivary hypertrophy, had a lesion somewhere in the dentato-olivary pathway via the brachium conjunctivum and contralateral central tegmental tract.

All the cases for which pathoanatomical data are available belong to the group with symptomatic RPM. To our knowledge no autopsy on a patient with essential RPM has so far been reported. Therefore any suggestions that transfer the pathoanatomical situation in symptomatic RPM to cases with essential RPM are speculative, especially as lesions within the brainstem or cerebellum as the prerequisite for hypertrophic degeneration of the inferior olive are unlikely as the patients have no additional clinical symptoms.

DISCUSSION

Although RPM has been regarded as a well-defined syndrome, the present data provide evidence that essential RPM should be separated from symptomatic RPM as a distinct clinical condition. This hypothesis may appear strange since RPM was first described

more than 100 years ago. Many single cases with RPM of unknown aetiology have been published, but only the collected data from many such patients demonstrate that they represent a clinical entity rather than a medical curiosity. We therefore felt justified in collecting cases from the literature, which of course represent a heterogeneous population as the individual cases have been reported with very different degrees of accuracy. We overcame this difficulty by selecting criteria that are relatively independent of the observer.

Clinical similarities and differences between essential RPM and symptomatic RPM

The present data are in favour of our hypothesis that essential RPM represents a separate clinical condition. Table 2 summarizes the main results. Some of them are self-evident, whereas others deserve some comment.

Of the features which are shared by essential and symptomatic RPM, the first is the rhythmic jerking of the soft palate. Although a number of different muscles may cause movements of the soft palate (Brodal, 1981), it is not known if the jerks differ between

TABLE 2 CRITERIA SEPARATING SYMPTOMATIC AND ESSENTIAL RHYTHMIC PALATAL MYOCLONUS

	<i>Symptomatic RPM</i>	<i>Essential RPM</i>
Aetiology	Cerebrovascular and degenerative disease, encephalitis, MS, trauma, others	Unknown
Neurological examination	Mostly brainstem/cerebellar symptomatology	Normal (except RPM)
Age at onset (yrs, mean $\pm$ SD)	45.1 $\pm$ 17.3	24.8 $\pm$ 12.9
Sex ratio (male:female)	2:1	1:1
Presenting complaint	Usually not related to RPM	Mostly earclick
Muscle territory involved	Frequent extrapalatal involvement, rarely earclick	Never nystagmus or extremity tremors, mostly earclick
Frequency (mean $\pm$ SD)	139 $\pm$ 51	107 $\pm$ 41
Duration of the hyperkinesia	Lifelong	Mostly persistent, remissions may occur
Prognosis	Related to underlying disease	Unknown. No evidence for reduction of life expectancy
Cessation during narcosis	No (4 cases)	Yes (4 cases)
Cessation during coma	No (13 cases)	Unknown
Cessation during sleep	No (29 cases), yes (2 cases)	No (5 cases), yes (5 cases)
Pathology	Mostly hypertrophic degeneration of the inferior olive	Unknown

the conditions. Secondly, both sides of the brainstem-innervated muscles seem to be involved to the same extent in both conditions. In some extrapyramidal diseases a unilateral distribution is found more often in symptomatic than in idiopathic cases (Marsden, 1988) but obviously not in symptomatic and essential RPM. This result has to be considered with some reservation as it is often difficult to decide whether a certain brainstem muscle is involved or not. Future investigations should, therefore, focus more precisely on this question, if possible together with EMG recordings. Thirdly, the duration of the hyperkinesia did not differ for symptomatic and essential RPM. Although remissions rarely occur in essential RPM, the present data confirm the earlier statement (Schenck 1965; Lapresle, 1979) that palatal myoclonus is a longstanding and mostly a lifelong disease.

It was the aim of our study to delineate the clinical picture of essential RPM. Some highly and some less significant differences from symptomatic RPM were found. In the essential form the hyperkinesia is obviously not a symptom of an underlying and often progressive disease. This seems evident as the patients develop no further signs or symptoms of neurological disease other than palatal myoclonus, despite the long course of the disease. It should be added that an appropriate observation period is required before accepting a diagnosis of essential RPM, because at least 1 case has been published with initially isolated RPM but later developing a brainstem tumour.

The incidence of essential RPM is obviously low, but it cannot be estimated on the basis of the available data. Even the ratio between essential and symptomatic RPM, which is 1:3.5 in the present collection, could be considerably biased, as it cannot be excluded that patients with essential RPM exist who do not suffer from earclicks and therefore have no reason to contact physicians. The only tentative argument militating against the latter view is the fact that many neurologists include inspection of the soft palate in their routine investigation without detecting cases with essential RPM without earclicks.

The typical complaint of the patients with essential RPM is a continuing rhythmic earclick as the only manifestation of subjective distress. As earclicks are rare in symptomatic RPM we conclude that this is the cardinal symptom of essential RPM. Other diseases associated with rhythmic ear sounds such as arteriovenous malformations can easily be distinguished by the character of the noise, the synchrony with heart beat and the lack of palatal hyperkinesia.

The muscles involved in the hyperkinesia differ significantly in essential and symptomatic RPM. In essential RPM only brainstem-innervated muscles (except for the eye muscles) have been observed to contribute. On the other hand, conjugate movements are a frequent and extremity tremor is a rare manifestation in symptomatic RPM. Hence both conditions differ in that a possible involvement of supranuclear motor centres may be present in symptomatic but not in essential RPM. This observation, as well as the lower mean frequency of the hyperkinesia in essential RPM, is discussed later with respect to the pathophysiology of the syndromes.

The age at onset of the hyperkinesia is another strong argument separating essential from symptomatic RPM. The means differ by about 20 yrs and the onset of essential RPM after the age of 40 yrs is extremely uncommon.

The sex distribution between males and females was a further parameter differing significantly between essential and symptomatic RPM. Whereas the patients with

symptomatic RPM had a clearcut male preponderance, those with essential RPM showed an equal sex distribution. In symptomatic RPM the general male predominance is due to patients with lesions of vascular origin, trauma and 'other symptomatic aetiologies', whereas the remaining symptomatic aetiologies had a balanced male/female distribution. We conclude from these observations that at least circumscribed brainstem infarcts manifesting with RPM alone are most unlikely as an unrecognized cause for essential RPM. A second aspect of these data will be mentioned. It has been suggested especially in the older literature that essential RPM might be a conversion symptom of hysterical origin, but as these are considered to occur more frequently in females, apart from other arguments, the balanced sex distribution is not in favour of a psychogenic origin.

Finally, the extent to which the rhythmicity of RPM can be modulated seems to differ between essential and symptomatic RPM. The latter seems to be resistant even to coma and narcosis, whereas essential RPM ceases during narcosis. In cases of essential RPM clearcut remissions have been described but never in the symptomatic form. All the extrapyramidal hyperkinesias such as tremors, tics, chorea and myoclonus cease during coma, narcosis and even sleep (Bergman *et al.*, 1953). Both essential and symptomatic RPM obviously may represent exceptions to this general rule, although further careful sleep recordings are necessary. The unique role that RPM holds in comparison with all other movement disorders as to its automatic rhythmicity mainly stems from the observation of cases with symptomatic RPM. These characteristics are either not found to the same extent in the essential form or they are not yet firmly proven.

We conclude that essential RPM is a nonprogressive monosymptomatic disease whose symptoms can severely inconvenience the patients but which is not life-threatening. In this respect it is comparable to other extrapyramidal diseases of unknown origin, for example, essential tremor. The above mentioned criteria are sufficient to assign an individual patient either to essential or symptomatic RPM. The proposed definition of the syndrome of essential RPM therefore seems plausible.

Considerations on the pathophysiological mechanisms in RPM

The vivid interest of many neurologists in such a rare movement disorder as RPM is supported by the expectation that general principles of rhythmic movement disorders can be studied in this condition. In fact, RPM is the only rhythmic movement disorder for which the presumed central oscillator can be convincingly located within the hypertrophically degenerated inferior olive. Moreover, the lesion causing this degeneration has been firmly established within the pathway from the dentate nucleus to the contralateral inferior olive (Rondot and Ben Hamida, 1968). Several attempts have been made to explain the development of rhythmic hyperactivity on the basis of these anatomical findings.

The first proposes the release or disinhibition of different primitive rhythms such as gill breathing which were suppressed when life went ashore. It is assumed that normally these primitive movements are suppressed by phylogenetically younger control systems. If the latter are destroyed the older rhythmicity was assumed to become uncovered (Yakolev, 1956). Yet it has already been emphasized (Schenck, 1965) that the territory of muscles involved in RPM is not related to any of these proposed primitive movements. Furthermore, it is hard to believe that the rhythmicity of a physiological movement such as gill-breathing is as independent from external influences as is RPM.

The second attempted explanation proposes rhythmicity of the basis of denervation supersensitivity of the inferior olive cells (Matsuo and Ajax, 1979). It is believed that receptors which lose their normal synaptic input, for example, following destruction of the dentato-olivary pathway, become hypersensitive to normal amounts of free transmitter within the CNS. It is hard to explain the rhythmicity of RPM on this basis.

Thirdly, a more recent explanation is based on a wealth of careful investigations in animals (Llinás, 1984). It has been shown that some cell groups within the CNS are able to produce rhythmic synchronized discharges under special conditions. So far this is established for the thalamus (Steriade and Deschenes, 1984) and the inferior olive (Llinás, 1984). For the latter, Llinás and Yarom (1986) have shown that a series of changes of membrane conductance to calcium (the 'low-threshold' calcium spike) and the calcium dependent potassium conductance at somatic and dendritic levels may cause an oscillatory mode of activity of inferior olive cells. The synchronization of rhythmic activation among different inferior olive cells is believed to be generated by the gap junctions (Sotelo *et al.*, 1977) between them which are known to mediate an electrotonic coupling (Llinás *et al.*, 1974; Llinás and Yarom, 1986). These findings were obtained in slice preparations, in the isolated brainstem preparation (Llinás and Mühlethaler, 1988) and in the intact animal (Sinton *et al.*, 1989) and are not clearly defined in man. Nevertheless, this model could explain the findings in RPM if some additional assumptions are made (Llinás, 1984; Yarom, 1989).

How can the present results be reconciled with these postulated mechanisms? The results show that all the relevant data on which the postulated mechanisms of RPM are based, such as the pathology or special resistance of the rhythmicity to external influences, are obtained from cases with symptomatic RPM. Therefore, strictly speaking, the theories on the pathophysiological mechanisms of RPM should be restricted to this form until comparable data are available for essential RPM. Nevertheless, it is of interest to discuss the impact of the suggested distinction on the pathophysiology of RPM even in a hypothetical form. The different muscles involved in the hyperkinesia and the different frequencies found for essential and symptomatic RPM stimulate such a discussion. The most striking finding is the frequent occurrence of earclicks and the failing access to supranuclear motor centres of gaze and limb muscles in essential RPM, as far as this can be deduced from the clinical investigation.

The earclick is most probably produced during movements of the eustachian tube as revealed by sonotubometry (Slack *et al.*, 1986). The click is either due to the walls of the eustachian tube snapping together (Pulec and Simonton, 1961) or, more likely, during opening due to the sudden breaking of the surface tension holding the walls of the tube together (Slack *et al.*, 1986). In both cases it would be related to rhythmic activity of the tensor veli palatini which is responsible for tube opening (Hollingshead, 1968). Palatal myoclonus could be associated with earclicks if the tensor veli palatini is involved but not if other palatal muscles cause the palatal jerks. Animal experiments suggest that at least four different motor nuclei contribute to the motor innervation of the soft palate. These motor nuclei are the ambiguous nucleus (levator palatini), trigeminal nucleus (tensor veli palatini), facial nucleus (median and paramedian muscles) and hypoglossal nucleus (palatopharyngealis and palatoglossus) (Strutz *et al.*, 1988). Hence essential RPM involves one or several motor nuclei in the brainstem including part of the trigeminal nucleus (tensor veli palatini), but symptomatic RPM includes this part

of the trigeminal nucleus only rarely. On the other hand, it shows frequent involvement of supranuclear motor centres as is shown by the involvement of conjugate eye movements (pendular nystagmus) or time-locked tremors of the limbs, which are never seen in essential RPM. This differential involvement of muscles could serve as an argument for different oscillators in the two conditions. A further tentative argument favouring different oscillators is the observation of a bimodal distribution of the jerk frequencies in essential and symptomatic RPM. Although it has been suggested that different frequency bands may be covered by oscillating inferior olive cells (Yarom, 1989), the alternative explanation by different oscillators cannot be excluded. Recently, such alternative oscillators have been proposed for different reasons (Kane and Thach, 1989).

Many arguments favour the traditional hypothesis that rhythmicity is produced by the degenerated inferior olive cells in symptomatic RPM. Essential RPM could either be based on a similar mechanism or on a different oscillator. As we have no clinical hints of an anatomical lesion in essential RPM, it seems possible that a 'chemical' denervation due to unknown transmitter changes may be involved. This could provide a link between these two conditions which also is anticipated in other movement disorders occurring in symptomatic and essential forms (Marsden, 1988). In that case, future investigations will have to explain which principles govern the involvement of different muscles in RPM. The well-known somatotopic organization of the inferior olive (Armstrong, 1974; Beitz, 1976; Brodal, 1981) could be responsible. Only part of it could undergo hypertrophic degeneration (Gautier and Blackwood, 1961; Lapresle and Ben Hamida, 1968) and thereby somatotopic connections could determine the extent of muscles involved in the rhythmic movements. On the other hand, the pathways distributing the underlying discharges could be different in the two conditions. No firm data are available to enable comments on this question. The alternative assumption of a different oscillator in essential RPM is supported by some of the present results. Future investigations with magnetic resonance imaging, positron emission tomography and careful electrophysiological investigations may further elucidate these open questions.

We conclude that our data support a separation of the clinical condition of essential RPM from the already well-known symptomatic RPM. Concerning the pathophysiology, there are some arguments favouring the inferior olive as the pacemaker in symptomatic RPM. For essential RPM the same or another pacemaker in the brainstem could be active. We hope that the suggested distinction between essential and symptomatic RPM will stimulate future investigations into this rare condition which, nevertheless, is of importance for the understanding of the rhythmic hyperkinesias in general.

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ADDENDUM

At the First International Congress of Movement Disorders, Washington, D.C., April 1990, the majority of participants agreed to term 'palatal myoclonus' in future as 'palatal tremor'. We fully agree with this new terminology (*see* Introduction) and propose to term the two conditions delineated in the present paper as 'symptomatic' and 'essential' palatal tremor.

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APPENDIX 1

Check list for the investigation of reported cases

- | | |
|--|---|
| 1 Year of publication | 11 General neurological examination |
| 2 Sex | —normal |
| 3 Age (reported) | —CNS or cranial nerve disease |
| 4 Duration of RPM | —spinal or peripheral nerve disease |
| 5 Delay between CNS lesion and appearance of RPM | (except cranial nerves) |
| 6 Fluctuations of RPM | 12 Muscles contributing to RPM |
| 7 Remissions | 13 Frequency of RPM |
| 8 Preexisting complaints—related to the hyperkinesia | 14 Modification of frequency |
| —related to the underlying disease | 15 Objective earclicks |
| —others | 16 Nystagmus (related to RPM) |
| 9 Birchick | 17 Aetiology |
| 10 Oscillopsia | 18 Therapeutic attempts |
| | 19 Results of pathomechanical investigation |

APPENDIX 2

*Aetiological classification of case reports of RPM**Vascular origin*

Alajouanine *et al.*, 1935
 Al-Wardi *et al.*, 1975
 Arnold *et al.*, 1960
 Bender *et al.*, 1952
 Bollinger *et al.*, 1974
 Chokroverty and Barron, 1969
 Cooper JC, 1958
 Davison *et al.*, 1936
 Day *et al.*, 1986
 Deroux MJ, 1936
 Deroux *et al.*, 1966
 Deschêl *et al.*, 1986
 Dobson and Riley, 1941
 Fox *et al.*, 1926
 Freeman W, 1933
 Freytsch B, 1928
 Gamber and Blackwood, 1961
 Gulpin A, 1931
 Grasty *et al.*, 1982
 Grill and Lacroix, 1932
 Guillemin and Thorel, 1932
 Harrison and Brown, 1967
 Harrison *et al.*, 1957
 Hoffman HL, 1953
 Jacobs and Bender, 1976
 Jordan *et al.*, 1977
 Kozzo JR, 1986
 Khanna *et al.*, 1980
 Klien H, 1907
 Koeppe *et al.*, 1980a
 Krul P, 1955
 Kuzachi *et al.*, 1985
 Lapresse and Ben Hamda, 1965
 Lawrence and Lagiboute, 1975
 Lévy G, 1925
 Lhermitte *et al.*, 1935
 Lhermitte and Dronson, 1937
 Lhermitte and Segwald, 1941
 Lynn AS, 1973
 McBride, 1903
 MacKinnon DM, 1968
 Mastaglia *et al.*, 1974
 Mascetti *et al.*, 1984
 Matsuo and Ajua, 1979
 Monaghan *et al.*, 1983
 Moritz W, 1939
 De Monner and Junot, 1937
 Murphy and Langworthy, 1939
 Nagata and Narabayashi, 1984
 Nakada and Kwon, 1986
 Nathanson M, 1956
 Nicoloso *et al.*, 1938
 Oates DL, 1957
 Ovulacq *et al.*, 1987
 Rao and Katana, 1969
 De Reynier J-P, 1957
 Rhoo *et al.*, 1974
 Riley and Brock, 1933
 Ronney *et al.*, 1927
 De Savitch E, 1936
 Schott *et al.*, 1965
 Shuttleworth *et al.*, 1985
 Secard *et al.*, 1928
 Settg and Haskovec, 1939
 Tabachnick *et al.*, 1972
 Towdall RD, 1958
 Thibaut and Monges, 1961
 Yap *et al.*, 1968

Case 4
 Case 1
 Cases 1,2,3,5,6
 Cases 2,3,4
 Case 1

Case 1
 Cases 1,2,3,5,6
 Cases 1-4
 Cases 1,2
 Cases 1,2
 Case 2
 Case 15
 Case 1
 Cases 1,10,11,14,17
 Cases 1,2,4

Case 6
 Case 2
 Cases 1,2
 Cases 1,3,4

Case 2

Cases 1,2

Case 2
 Cases 1,4
 Case 6
 Case 32

Case 3
 Case 1
 Cases 1,2
 Cases 1,3,4
 Cases 1-5
 Cases 6,8,9,10,12

Case 2

Cases 1-4
 Case 1

Case 1,2

Syphilitic vasculitis

André-Thomson and Long-Landrey, 1924
 Bender *et al.*, 1952
 Pierre-Bonhien and Garzin, 1937, 1940
 Garzin and Jacquemot, 1937
 Schenck E, 1965

Case 4

Case 1

Thromboses

Ablin and Schwartz, 1963
 Bender *et al.*, 1952
 Ebor *et al.*, 1975
 Garzin *et al.*, 1971
 Harbord and Brumlik, 1967
 Harrison and Brown, 1967
 Harrison *et al.*, 1957
 Kawasumi *et al.*, 1969
 Lynn AS, 1973
 Moritz W, 1939
 Nathanson M, 1956
 Orzechowski, 1932
 Riley and Brock, 1933
 De Savitch *et al.*, 1937

Cases 1,2
 Case 8

Case 2

Cases 13,15
 Cases 6, 7

Case 3

Case 2

Cases 2,3,4

Case 3

Degenerative diseases

Crozon and Christophe, 1936
 Leger *et al.*, 1986
 Mastaglia *et al.*, 1974
 Mascetti *et al.*, 1984
 Nagata and Narabayashi, 1984
 Tabachnick *et al.*, 1972
 Tatematsu J, 1968

Case 3

Case 4

Case 2

Case 2

Encephalitis

Bojnov and Lokova, 1968
 Grasty *et al.*, 1982
 De Monner and Junot, 1937
 Rohner *et al.*, 1966
 Schenck E, 1965

Case 18

Case 2

Case 3

Multiple sclerosis

Chokroverty and Barron, 1969
 Deroux MJ, 1938
 Gamber and Blackwood, 1961
 Grasty *et al.*, 1982
 Harrison and Brown, 1967
 Harrison *et al.*, 1957
 Lynn AS, 1973
 Mooren *et al.*, 1962
 Nathanson M, 1956

Case 1

Case 5

Case 12

Case 3

Case 4

Case 1

Case 7

Trauma

Alajouanine *et al.*, 1956
 Arnold *et al.*, 1960
 Bender *et al.*, 1952
 Bonchayer *et al.*, 1969
 Deschêl *et al.*, 1986
 Hanne and Lehan, 1959
 Heller MF, 1962
 Jacobs *et al.*, 1981
 Loebell H, 1937
 Magnusson *et al.*, 1977
 Mastaglia *et al.*, 1974
 Matsuo and Ajua, 1979
 Michel *et al.*, 1972
 Obrador and Sanchez, 1932

Case 2

Case 7

Cases 1,2

Case 2

Case 1

Case 1

Case 2

Case 33

Riley and Brock, 1933	Case 1	Devason <i>et al.</i> , 1936	Case 1
Shaddock <i>et al.</i> , 1972	Cases 1,2	Fain M., 1953	
Stern MM., 1949		FitzGerald DC, 1984	
Stolberg <i>et al.</i> , 1965	Case 2	Freund EM., 1956	
Turco <i>et al.</i> , 1977		Prodromou C, 1904	
Zander <i>et al.</i> , 1965	Cases 1,2	Gates A., 1957	Cases 1,3,4
<i>Others</i>		Goldham and Meyerson, 1895	
Alyoussou <i>et al.</i> , 1938, 1944		Gupta <i>et al.</i> , 1972	
Alfaro VR, 1950		Heller MP, 1962	Case 2
Amico <i>et al.</i> , 1959	Case 3	Herrmann and Brown, 1967	Case 9
Barrié <i>et al.</i> , 1926		Hughes J., 1965	
Baruk <i>et al.</i> , 1945		Jacobs <i>et al.</i> , 1981	Case 2
Bondy and Guillard, 1973		Kaufman D., 1894	
Donny-Browne D, 1934		Kayed <i>et al.</i> , 1983	Cases 1,3
Dobson and Riley, 1941	Case 1	Köhler O., 1955	Case 3
Ekblom and Karlberg, 1967		Köpper, 1873	
Pederman and Sommer, 1970		Kwo and Strobes 1972	Cases 1,2
Freystadt B, 1928	Case 3	Laignol-Lavastrie and Lergoux, 1929	
Garcia <i>et al.</i> , 1966		Leibowicz A, 1966	Cases 1,2
Garcia <i>et al.</i> , 1945	Case 2	Leventon <i>et al.</i> , 1968	Cases 1-5
Herrmann <i>et al.</i> , 1957	Cases 5,8	Litman and Hassenman, 1982	
Kartin <i>et al.</i> , 1974		Lynn AS, 1973	Case 5
Kayed <i>et al.</i> , 1983	Case 2	MacKinnon DM., 1968	Case 1
Krebs <i>et al.</i> , 1932, 1951		Messer-Ewert <i>et al.</i> , 1970	Case 1
Meuron <i>et al.</i> , 1962	Case 3	Mollerat <i>et al.</i> , 1937	
Nathanson M., 1956	Cases 5,11	Moore <i>et al.</i> , 1962	Cases 2,4,5
Radenmacher and Holmsmoortel, 1939		Nardi and Dell'Agho, 1964	
Rabito and Haldanes 1979	Case 1	Parnes SM., 1977	
Raboul <i>et al.</i> , 1967		Pearson and Barnes, 1948	
Rodot <i>et al.</i> , 1965		Politzer A., 1870	
Schoeck E., 1965	Case 2	Pulec and Samonten, 1961	Cases 1,2
Sono <i>et al.</i> , 1984		Rabito and Haldanes 1979	Cases 1,2
Strubano <i>et al.</i> , 1983	Case 1	Ruter K., 1973	
Stolberg <i>et al.</i> , 1965	Case 2	Sargent <i>et al.</i> , 1970	Cases 1,2
Toland <i>et al.</i> , 1984		Schaefer, 1939	
<i>Excluded</i>		Schoeck E., 1965	Case 4
Alfaro VR, 1950	Cases 1,2	Schubert and Neuss, 1959	Case 2
Asby <i>et al.</i> , 1953		Schwager, 1896	
Bjork H., 1954	Cases 1-4	Schwartz, 1867	
Boock O., 1867		Toland <i>et al.</i> , 1984	Case 1
Bogner A., 1956		Tyler R., 1953	
Burnett H., 1876		Valentin A., 1904	Case 2
Campes G., 1968		Vah E., 1905	
Cassara W., 1969	Case 3	Williams <i>et al.</i> , 1978	
Chadwick and Macbeth, 1953	Cases 1-4	Wirth G., 1962	
		Yagin <i>et al.</i> , 1985	
		Zöllner F., 1942	Case 25

EXPERIENTIAL PHENOMENA OF TEMPORAL LOBE EPILEPSY

FACTS AND HYPOTHESES

by PIERRE GLOOR

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SUMMARY

Experiential phenomena that occur in temporal lobe seizures and can be reproduced by electrical stimulation of temporal lobe structures typically encompass perceptual, mnemonic and affective features, either in combination or in isolation, which commonly relate to the patient's individual past experience. These phenomena raise interesting questions concerning brain mechanisms involved in human psychophysiology. The anatomical substrates for the evocation of these phenomena are widely distributed within the temporal lobe and include temporal isocortex and limbic structures (amygdala, hippocampus and parahippocampal gyrus). Arguments are presented which indicate that experiential phenomena are positive expressions of temporal lobe and limbic function and do not result from its ictal paralysis. Recent concepts of parallel distributed processing (Rumelhart and McClelland, 1986) and the importance of parallel distributed cortical networks for higher cognitive functions (Goldman-Rakic, 1988*a, b*) provide a theoretical framework on which a hypothesis explaining experiential phenomena can be based. In conformity with these concepts the hypothesis assumes that temporal lobe epileptic discharge or electrical stimulation of temporal lobe structures can induce the elaboration of patterns of excitation and inhibition in widely distributed neuronal networks, some of which are capable of forming a specific matrix representing the substrate of a given experience. Neuronal networks engaged in parallel distributed processing (1) have the capacity to recreate the totality of a given experience when only a fragment of the network is activated, and (2) they tolerate a great deal of degradation by random inactivation of its components or by interference through random noise without serious loss of information content. These features are compatible with the assumption that localized epileptic neuronal discharge or electrical stimulation involving some temporal lobe structures could create a matrix representing features of individual experience of the kind activated in the course of temporal lobe seizures. Such an experience could, up to a certain limit, resist the degrading influence of mounting noise which inevitably must attend seizure discharge.

INTRODUCTION

Among the manifestations of temporal lobe epilepsy psychic phenomena are the most intriguing. They are the only manifestations evoked by cerebral seizures which relate to the patient's personal identity. Hughlings Jackson (1879, 1888) made the first systematic study of them and called them 'the *most* [*italics by Jackson*] elaborate psychical state(s)'. Penfield (1938) made the important discovery that these mental phenomena can be reproduced by electrical stimulation of the temporal lobe in epileptic patients during surgical procedures performed for the relief of their seizures. He called 'experiential' those mental phenomena that 'have to do with the past' and 'interpretive'

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those that 'have to do with the present' (Penfield, 1954, 1958*b*). Among the latter he included illusions and emotions. In our study of 1982 (Gloor *et al.*, 1982) we used the term 'experiential' in a broader sense and included the interpretive responses as defined by Penfield under this rubric. This broader definition will be used in the present paper. Attempts to answer the question as to how temporal lobe seizure discharge or electrical stimulation of temporal lobe structures can elicit such mental phenomena and in particular a reactivation of past personal experience may help us to understand human psychophysiology better.

DEFINITION AND CHARACTERISTICS OF EXPERIENTIAL PHENOMENA

Typically experiential phenomena, when fully expressed, create in the patient's mind experiences, usually from his personal past, that have a compelling immediacy similar to or sometimes even more vivid than those occurring in real life. It is this quality of being like a real life experience which justifies the term 'experiential' and its extension to phenomena which Penfield (1954, 1958*b*) called 'interpretive'. Experiential phenomena are, however, not universal features of temporal lobe seizures and their complexity varies from case to case. They typically combine elements of perception, memory and affect. This distinction is somewhat artificial for, as in real life, often all these three features are encompassed in a unified subjective experience (Gloor *et al.*, 1982). Sometimes, however, only perceptual, mnemonic or affective fragments may be evoked in isolation. Detailed descriptions of experiential phenomena have been given by Jackson (1879, 1888), Penfield (1938, 1954, 1955, 1958*b, c*), Penfield and Jasper (1954), Mullan and Penfield (1959), Penfield and Perot (1963), Weingarten *et al.* (1976), Halgren *et al.* (1978) and Gloor *et al.* (1982). On reading these accounts there is a remarkable similarity in the descriptions given by patients who lived a century apart and came from vastly different cultural backgrounds.

The most common perceptual phenomena are those involving the visual and auditory modalities in the form of illusions or, more importantly, hallucinations. In the latter instance, the patient may see a scene, a face, or hear a voice or a piece of music being played. The content of these hallucinations usually appears familiar to him, although he may not always be able to identify it specifically. Olfactory and gustatory hallucinations are less common and their true experiential character is debatable, since they are usually not described by the patient as a specific olfactory or gustatory sensation or as an evocation of a past experience. Somatosensory hallucinations having experiential qualities are practically unheard of, although vague somatosensory phenomena, often cephalic, are common in temporal lobe seizures.

Memory phenomena of two kinds occur in temporal lobe attacks. First, there may be actual recall of a past event or situation, usually more vivid and intrusive than a commonplace recollection or secondly, there may be a feeling of recognition, of familiarity or reminiscence. Recall of a past event and the feeling of familiarity may occur together as they commonly do in real life, but each may also occur in isolation. If the feeling of familiarity or recognition occurs in isolation, it is often inappropriately attached to the present, creating the illusion that the present is like the re-enactment of a past situation or event, the so-called *déjà vu* illusion. The patient is, however, always aware and usually struck by the incongruity and illusionary nature of this experience.

There are intermediate situations where the patient experiences a feeling of familiarity and a strong feeling that he is just about to recall some specific event from his past, but that memory never surfaces, a sort of 'tip of the tongue' phenomenon. Under these circumstances the present, however, is not experienced as familiar. The best description of the subjective quality of this phenomenon is still that given by Hughlings Jackson's patient, Dr Z., which Jackson reproduces verbatim in his 1888 paper.

Among affective responses, fear is by far the most common. It may range from mild anxiety to outright terror. It is often associated with a visceral sensation usually referred to the stomach or chest which may also occur without an affective response. Less commonly, any one among the full array of human affective states may be evoked, such as sadness, loneliness, embarrassment, guilt, anger, anticipatory excitement, mirth, sexual excitement and happiness.

Having briefly reviewed these positive characteristics of experiential phenomena, it is important to point out that they typically also lack some features that are ordinarily part of real life experiences. Thus the experiences do not move forward in time, with the single exception of the hallucination of hearing music. Scenes are static; they do not evolve, there is no story to be told. The patient remains passive and does not feel that he actively participates in the hallucinated scene. Perceptual detail may be fragmentary or lacking in spite of a subjective feeling of vividness of the experience. The auditory hallucination of hearing a voice is almost always without semantic content, even though the voice may sound familiar and may be identifiable. The affective tone of the voice, however, is often recognized. It is not so much cognitive detail that endows these fragmentary experiences with a sense of reality, but the feeling of 'being there', as one of our patients expressed it.

To those familiar with Penfield's writings, some of the above statements appear to contradict his observations. However, the contradictions reside not in the observations themselves, but in the interpretations given to them. The actual descriptions given by the patients in his and our series are identical in kind. There are two of these contradictions, both deserving some comment.

The first is that the hallucinated experiences were said by Penfield (1947, 1954, 1955, 1958*b*; Penfield and Perot, 1963) to move forward in time at a natural tempo. All the examples given by Penfield in support of this view were musical hallucinations in which the patient, when requested to do so, hummed or sang the hallucinated tune while the stimulation was on. None of the other auditory and none of the visual hallucinations showed any forward motion in time. Why then was this feature restricted to musical hallucinations? A possible explanation is that if a patient hallucinates hearing a piece of music and is then asked to hum it, he would most likely do so at a natural tempo.

The second contradiction is that according to Penfield (1952, 1954, 1955, 1958*b*; Penfield and Perot, 1963) the evoked remembered events are a detailed record of past conscious experience, more detailed than memories than one is able to recall voluntarily, since the experiential hallucinations contain specific features that would have been unavailable to voluntary recall. This led Penfield to postulate that the actual record of a consciously experienced past event was reproduced with all the details of which the patient had been aware at that time. In my judgement the descriptions given by Penfield's patients do not support this statement. They are as fragmentary as those we have recorded. What may lead to the conclusion that all details of a past experience have been called

forth, is that the patient is often quite specific about the identity of the event or situation that has been evoked and may indeed be able to report *some* very specific details that would elude voluntary recall. The evocation of such details, coupled with a subjective vividness of the experience confers upon it the illusion of recreating past reality.

I shall now describe and analyse in detail a particularly illuminating observation made in the course of a stereotaxic depth electrode exploration of the temporal lobes in a 22-yr-old epileptic patient. The patient had been instructed to let us know if he felt something, when told that the stimulation had been turned on. When, after many negative stimulations in superficial and sulcal temporal isocortex, the right amygdala was stimulated for 2.8 s at the low intensity of 1 mA, the patient immediately said, 'Yes'. When asked what he had felt, he found it difficult to describe; it was a feeling like falling into water. When asked to elaborate, he replied that it was as if something had covered his eyes, nose and mouth. To the question whether the feeling was scary, he answered 'Yes and no'. He also described it as one of strangeness and it recalled memories of small attacks he had had. There was no electrical after-discharge in the stereotaxically recorded EEG, which included that from the stimulated amygdala. Stimulation was then repeated at the same intensity for 2.4 s, but without warning the patient. He immediately exclaimed, 'Now', and then quite excitedly added, 'Could you do it again, doctor?' When asked why he wanted the stimulation repeated, he explained that when it began he had the words on his lips to describe the feeling, but then later could not do so. Again there was no after-discharge.

Stimulation at the same intensity was repeated once more without warning, but the duration was now 4.4 s. The patient opened his mouth with an astonished look, sat up and said that he now knew what it was. It was the feeling of being at a picnic in Brewer Park in Ottawa: 'A kid was coming up to me to push me into the water. It was a certain time, a big special day during the summer holidays and the boy was going to push me into the water. I was pushed by somebody stronger than me. I had experienced that same feeling when I had "petit mals" before'. He called it 'a bad feeling'. Again there was no after-discharge. On questioning, he said this had been a real event in his life when he was about 8 yrs old. He remembered some additional details such as how 'a big fellow' had pushed him under the water and kept his head submerged. Asked whether during the stimulation he had actually seen himself being chased by the 'big fellow', he said, 'No', but it was a feeling as if he had been there and was being chased. He believed this event had occurred shortly before his seizures had started.

Let us now consider some of the features of the experiential response elicited by amygdaloid stimulation in this patient. The first is their subjective quality and content. It was obvious to all who witnessed the stimulations that the patient was deeply affected by the experiences elicited by them. They were vivid and represented an amalgam of perceptual, mnemonic and affective elements. The perceptual features seemed to be mostly visual, perhaps also vaguely somatosensory (the feeling of something covering his face, reminiscent of water). The mnemonic element was evident as he experienced a re-enactment of a specific event from his childhood; he felt as if he was there again. The affective impact was equally obvious as the experience evoked a 'bad feeling'.

That the experience struck the patient as a re-enactment of the past and made him feel 'like being there', should not deceive us, however, into assuming that all the details of this earlier experience were 'replayed' in his mind in their original sequence with

all the attendant perceptual detail. The experience was not like the rerunning of a videotape. In fact, the patient's description lacked detail, it was fragmentary. The response to the first stimulation contained only the crucial element of a feeling reminiscent of falling into water. The patient had difficulty describing it, and only when asked to elaborate, did he explain that it was like something covering his eyes, nose and mouth. Thus it was not the primary sensory quality and the location on the body of this possibly somatosensory experience that immediately struck him, but rather the feeling of falling into water, presumably related to a specific event that he could not specify further at that time. This is very different from the way patients report somatosensory responses elicited by stimulation of the postcentral gyrus. The description they give of these are related primarily to an elementary sensory quality, such as 'tingling' or 'numbness', and to a specific location in the body, for instance 'tip of the tongue', 'right thumb', etc. (Penfield and Boldrey, 1937; Penfield, 1947, 1954, 1958c; Penfield and Rasmussen, 1950; Penfield and Jasper, 1954), but there is never a report of an experiential context, as for instance a feeling of being touched by someone that reminds the patient of a particular circumstance of his past.

A further interesting aspect of the fragmentary character of the experiences evoked in our patient was the fact that the first stimulation, in spite of eliciting a feeling of falling into water, was not sufficient to call forth the memory of the past event to which it was most likely connected and which was brought out only by the third stimulation. The patient's reaction to the second stimulation suggested that it evoked a subjective experience of reminiscence, of almost knowing what the 'feeling' was about, yet there was no retrieval of the specific memory connected to the 'feeling'. Thus a memory retrieval mechanism seemed to have been activated, but only incompletely.

The third stimulation, however, unlocked the access to that memory, that of a specific event from childhood that was dimly perceptible in the experiences elicited by the two preceding stimulations. Yet the patient still described it in a fragmentary manner, stressing its emotionally laden features. He did not tell a detailed story; the recollection of the event was reduced to a few of its essential elements: its locale and time and the fact that he had been physically abused by submersion into water by a stronger boy. There was no other detail and yet the experience had a subjective immediacy similar to that of the original event: it was 'as if I had been there'. One suspects that this vividness was conveyed by the affective impact of the remembered experience rather than by details of the perceptual scene as called forth by memory.

What, in fact, were the perceptual qualities of the experience? Was there a real visual hallucination? The impression on those of us who witnessed the patient's response to the stimulation and the way he described it, was that he most likely had experienced a visual hallucination. However, when questioned later he denied having seen himself being chased by the 'big fellow', but it was 'as if I had been there and was being chased'. Whether his experience was a true visual hallucination or merely a perceptually less specific but strong recollection of the past event, which he described primarily in visual terms, must remain an open question.

Anatomical substrates of experiential responses

Experiential responses occur virtually only in seizures arising from the temporal lobe and by no means in all of them. They can be elicited in some epileptic patients by electrical

stimulation in the temporal lobe but virtually never by stimulations applied to other regions of the cerebral cortex (Penfield, 1938, 1947, 1952, 1954, 1955, 1958a, b, c; Penfield and Rasmussen, 1950; Penfield and Jasper, 1954; Penfield and Perot, 1963). When Penfield and Perot (1963) reviewed all the stimulation responses that had evoked experiential phenomena, they found that most were elicited from the lateral temporal isocortex, with only few occurring in response to basal temporal isocortical, or mesial limbic stimulations in the region of the uncus. Most likely this distribution reflects a methodological bias, inasmuch as the lateral convexity cortex was stimulated more frequently than the mesial or deep structures of the temporal lobe (T. Rasmussen, personal communication). The most interesting observation made by Penfield and Perot (1963) was that showing some degree of topographical segregation between auditory and visual experiential responses on the lateral surface of the temporal lobe. The topographical specificity of the auditory responses was particularly striking. They were clustered along the first temporal convolution which is known to contain the auditory association areas (Milner, 1962; Shankweiler, 1966; Dewson *et al.*, 1970; Cowey and Dewson, 1972; Neff *et al.*, 1975; Strominger *et al.*, 1980; Pandya and Yeterian, 1985; Zatorre, 1985; Petrides and Pandya, 1988). The visual responses were evoked from more widespread regions of the temporal isocortex extending from the temporo-occipital junction to the temporal polar region. They were located in cortical regions known to be involved in higher-order visual perceptual functions (Milner, 1958, 1968; Kimura, 1963; Mishkin, 1966, 1972; Chow, 1961; Allman, 1977; Desimone and Gross, 1979; Gross *et al.*, 1981; Ungerleider and Mishkin, 1982; Mishkin *et al.*, 1983; Pandya and Yeterian, 1985). Both auditory and visual experiential responses were obtained more often with right than with left temporal isocortical stimulations.

When several years later we began our stereotaxic depth electrode investigations of epileptic patients, we were therefore surprised to find that virtually all the experiential responses we obtained were elicited by stimulation of the limbic structures of the temporal lobe and not of the temporal isocortex (Gloor *et al.*, 1981, 1982). The amygdala showed the highest incidence of positive responses, the temporal isocortex virtually none. The isocortical regions accessible to our stereotaxically inserted stimulating electrodes were, however, restricted to an anterior segment of the second temporal convolution and to sulcal cortex below it, mostly that within the superior temporal sulcus as well as cortex at the bottom of the sylvian fissure at the transition between temporal and insular isocortex. Suspecting that our results may have been skewed by a methodological bias opposite to that in Penfield's studies, this time in favour of limbic stimulation sites, we analysed 100 separate cases of cortical and deep temporal stimulations carried out more recently during surgical procedures under local anaesthesia. The techniques were similar to those used by Penfield and thus allowed for a wider range of sampling from surface cortical stimulation sites. In this series again experiential responses were more commonly elicited by limbic than by isocortical stimulations (Gloor *et al.*, 1982).

That affective responses could be elicited from the amygdala was not surprising. Most of these were not associated with an after-discharge or only with one confined to the area of stimulation and could therefore not be attributed to spread of the epileptic discharge to temporal isocortex. What we had not expected, however, was that perceptual hallucinations and mnemonic responses, both flashbacks and déjà vu illusions, were also elicited predominantly by amygdaloid stimulation (Gloor *et al.*, 1981, 1982). If

anything, the concentration of positive stimulation points in the amygdala was even more striking for these perceptual and mnemonic responses. Again the results cannot be explained by invoking spread of epileptic discharge to temporal isocortex, since most of these responses occurred without an after-discharge, or with one locally confined to the amygdala without further spread. It therefore seemed obvious that the amygdala was a very effective site for the elicitation of every kind of experiential response.

Still, these observations do not invalidate Penfield's findings, and one must therefore conclude that experiential responses can be elicited by stimulations applied to temporal isocortex as well as to the temporal limbic structures, particularly the amygdala. It is our impression, however, that they are more easily elicited by limbic stimulations.

Previous hypotheses concerning the mechanism of experiential phenomena

Having reviewed the features of experiential phenomena elicited either by temporal lobe epileptic discharge or by electrical stimulation of temporal lobe structures, one must seek an explanation of these observations. The first who put forward a hypothesis to explain these phenomena was Hughlings Jackson. In a footnote to his 1879 paper he stated 'that elaborate states are a result of removal of control of higher centres'. In other words, experiential phenomena result from a release of inhibition exerted by higher centres, their function being presumably interfered with by epileptic discharge. A similar explanation was given much more recently by Ferguson *et al.* (1969) and by Halgren *et al.* (1978) who speculated that subconscious, emotionally laden material is allowed to surface into consciousness because some inhibitory control normally exerted by limbic structures has been disrupted by epileptic discharge. The hallmark of these hypotheses is that they regard experiential phenomena as purely negative effects of brain stimulation.

Penfield held a different view. He accepted the possibility that epileptic discharge or electrical stimulation exerted positive effects by activating physiological mechanisms represented in temporal cortex (Penfield, 1952, 1954, 1955). Although he also assumed that the strictly local effect of stimulation was probably one of disruption or interference, he believed that this local discharge through physiological processes normally involved in memory mechanisms 'dromically' activated at distant sites what he called a 'replay' of the 'ganglionic record of past experience' (Penfield, 1955, 1958*b*, *c*). He proposed that epileptic discharge or discharges elicited by electrical stimulation could replay the record of past experience in great detail, in its natural sequence and at the natural speed of 'the stream of consciousness' (Penfield, 1954, 1955, 1958*b*). He likened it to the replay of a recording on a tape recorder. The argument marshalled by Penfield in favour of this hypothesis was based exclusively on his observation on hallucinations of music, as discussed earlier in this paper.

A new hypothesis

I would like to propose that experiential phenomena elicited by temporal lobe seizures or electrical stimulation of the temporal lobe are a positive expression of the functions of temporal lobe structures and do not reflect ictal interference with or paralysis of these functions. Two main arguments can be invoked in favour of this interpretation.

The first is related to epileptology and clinical neurophysiology. Experiential

phenomena in temporal lobe epilepsy are fleeting; they occur at the beginning of a seizure. They are a part of the patient's aura. They do not continue into the ictus for any length of time and are not present postictally. If they were caused by ictal paralysis of temporal lobe function, it would be expected that they would also be present postictally, as is the case for automatism, confusion and amnesia which as Penfield (1955) had pointed out are the true manifestations of ictal paralysis of temporal lobe function.

The second argument in favour of the experiential phenomena being positive expressions of temporal lobe function derives from the fact that the temporal association cortex and limbic structures are precisely those known to be the substrates for the functions revealed by experiential phenomena. Thus the formation of visual and auditory percepts, visual and auditory discrimination, the encoding of these features in long-term memory, and the attachment of affective significance to these perceptual and mnemonic phenomena are functions of temporal association cortex, hippocampus and amygdala (Klüver and Bucy, 1939; Scoville and Milner, 1957; Milner, 1958, 1962, 1968; Penfield and Milner, 1958; Chow, 1961; Downer, 1961; Mishkin, 1966, 1972, 1982; Weiskrantz, 1968; Dewson *et al.*, 1970; Cowey and Dewson, 1972; Gloor, 1972, 1978; Desimone and Gross, 1979; Strominger *et al.*, 1980; Gross *et al.*, 1981; Spiegler and Mishkin, 1981; Ungerleider and Mishkin, 1982; Mishkin *et al.*, 1983; Amaral, 1987; Squire, 1987*a, b*). Furthermore, these same temporal lobe structures are also involved in activating the recall of past experience. These concepts are in line with what is known about the flow of information through the temporal lobe. One of the main streams flows from the primary visual and auditory areas to visual and auditory association cortices in the anterior portion of the temporal lobe (Mishkin, 1966, 1972; Jones and Powell, 1970; Allman, 1977; Turner *et al.*, 1980; Ungerleider and Mishkin, 1982; Mishkin *et al.*, 1983; Pandya and Yeterian, 1985). Increasingly along this way perceptual functions of a higher order are elaborated, such as the definition of objects. From the anterior temporal isocortex this perceptual information is channelled through two separate streams towards the amygdala on the one hand and to the hippocampus on the other (Jones and Powell, 1970; Turner *et al.*, 1980; Spiegler and Mishkin, 1981; van Hoesen, 1981, 1982; Pandya and Yeterian, 1985). These two structures are in turn reciprocally interconnected. The hippocampus sets into motion the processes that consolidate the experience in memory (Scoville and Milner, 1957; Penfield and Milner, 1958; Mishkin, 1982; Amaral, 1987; Squire, 1987*a, b*), while the amygdala endows it with affective tone (Weiskrantz, 1956; Gloor, 1960, 1972, 1978; Jones and Mishkin, 1972; Spiegler and Mishkin, 1981). Considering the anatomical organization and the role of these structures in perception, memory and affect, it is illogical to assume that the reproduction of experiences known to be dependent upon the integrity of these structures should be a consequence of their ictal inactivation.

The reason for the reluctance to view experiential phenomena as a positive expression of neural activity produced by epileptic discharge or electrical stimulation is rooted in the belief that such activity is unphysiological and crude, and thus could not reproduce the temporal pattern and sequencing of neuronal discharges necessary for complex mental functions. However, this preconception rests on little objective evidence. Precise timing of neuronal discharge is not required for many complex functions of the central nervous system. It is the signal-to-noise ratio, that is, the elevation of discharge rate above the background firing level in specific neuronal populations, that carries the information,

not the sequence of action potentials as such. A simple example of this is the perceptual attribute of orientation of an edge which in the visual cortex is coded by an increased discharge rate within a specific neuronal population of an orientation column (Hubel and Wiesel, 1968). The same is true for cells attuned to more complex stimuli, like those found in the superior temporal sulcus which respond to the sight of faces (Baylis *et al.*, 1985).

I shall now propose a hypothesis which could account for the elicitation of experiential phenomena occurring in the early part of a temporal lobe seizure or in response to electrical stimulation within the temporal lobe. The hypothesis is based on the assumption that under normal conditions evocation of an experience depends on the formation of a specifically patterned matrix made up of excited and inhibited neurons dispersed within widely distributed neuronal populations in large areas of isocortex and of the limbic system. Such a matrix which encodes its perceptual, mnemonic and affective information can be thought of as 'representing' an experience and to be specific for it. What carries the specific information is not the activity of any single cell within this population, but the specific pattern of connectivity woven between the neurons which creates a distributed matrix of excitation and inhibition and is specific for the experience it 'represents'. I propose furthermore that an epileptic discharge within the temporal lobe at the onset of a seizure, when it has not yet become too diffuse or too intense, may be able to recreate a specific matrix that may be similar or identical to that normally encoding a natural experience. Repeated discharge through mechanisms of synaptic plasticity known to be affected by epileptic discharge (*see* review by Gloor, 1989) may have strengthened the interconnectivity of the neurons constituting such a matrix. The hypothesis requires that all or most of the structures involved in the formation of such a matrix are reciprocally interconnected, such that the information flow from sensory areas to association cortex and to limbic structures can be reciprocated by connections going in the reverse direction, specifically from hippocampus and amygdala to widespread isocortical regions. Recent anatomical investigations have shown this to be the case: efferent connections from the hippocampus through relays in the parahippocampal gyrus are known to reach widespread areas of temporal, parietal and frontal association cortex (Rosene and van Hoesen, 1977; van Hoesen, 1982). They are probably important for the consolidation of memory. Amaral and Price (1984) have shown how anterograde label injected into the amygdala is transported along efferent connections into widespread areas of the association cortex, particularly in the temporal lobe, reaching even the visual cortex in the occipital lobe. Such connections may be involved in affective recall of an experience, and Amaral and Price (1984) have suggested that such connections may play a role in the mechanism of experiential hallucinations.

The proposed hypothesis fits in with current theories of the function of parallel distributed cortical networks (Goldman-Rakic, 1988*a, b*), parallel models of associative memory (Anderson and Hinton, 1981; Kohonen *et al.*, 1981), and the notion of parallel distributed processing of information within the brain as a basis of learning and memory as put forward by Rumelhart and McClelland (1986).

The orderly arrangement and the multiplicity of these connections between cortical neurons is striking. A fundamental unit of organization of cerebral cortex is the cortical column about 300 μm in diameter, each consisting of a group of pyramidal cells and associated interneurons, and each having multiple but very specific ipsilateral and

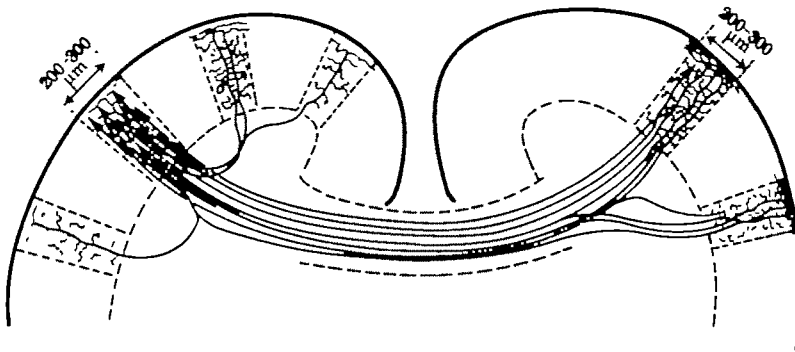


FIG. 1. Columnar organization of corticocortical connectivity through ipsilateral associational and contralateral callosal connections. There is a highly specific pattern of connections between columns of 200–300 μm in diameter: cells forming a column emit connections that terminate in multiple distributed similar distant columns. (Reproduced with permission from Szentágothai, 1978)

contralateral interconnections with other cortical columns (fig. 1) (Szentágothai, 1975, 1978; Goldman and Nauta, 1977; Goldman-Rakic and Schwartz, 1982; Eccles, 1984; Goldman-Rakic, 1988*a, b*). Each column emits multiple ipsilateral and contralateral connections sharply focused on other columns. Each column also has specific interconnections with patches of neurons in various thalamic nuclei, the striatum and in limbic structures (Goldman-Rakic, 1988*a, b*). In some instances cortical columns formed by projections from distant ones interdigitate with neighbouring columns which receive afferents from different distant columns with little overlap between them; in others there is overlap of projections within the same column but those from different sources project to different cortical layers (Goldman-Rakic, 1988*a, b*). Each column has its own specific pattern of connectivity which in general may be similar to that of a neighbouring one, but may differ in detail. Most of these connections are reciprocal. Such multiple interconnected columns thus have what could be called 'private' lines of intercommunication that are widely distributed over distant sites occupying frontal, parietal, and temporal association cortex, as well as limbic structures. They form complex interconnected nets as shown in fig. 2 taken from Goldman-Rakic (1988*a*) which portrays the mutual interconnections of frontal, parietal, temporal and limbic cortex. Thus distant areas of the cerebrum are interconnected in a specific mosaic pattern. Information received in one column can be distributed to a multitude of distant cortical, ipsilateral, limbic and thalamic neuronal patches. All these mutually interconnected areas can thus be imagined as sharing some common information.

Interconnectivity in such networks can presumably be modified and shaped by experience, inducing plastic synaptic changes (Eccles, 1984). The resulting complexity of activities within such a system staggers the imagination, but it is important to realize that information passed along within such a tightly interconnected network does not result in chaos, but forms a highly structured, albeit highly complex matrix of distributed excitation and inhibition. This can be quite effectively depicted by the diagram in fig. 3 taken from Eccles (1984). In this diagram each circle represents a cortical column. Taking the liberty of attaching a somewhat more down-to-earth interpretation to this diagram than had been intended by Eccles, let us imagine that the black columns are

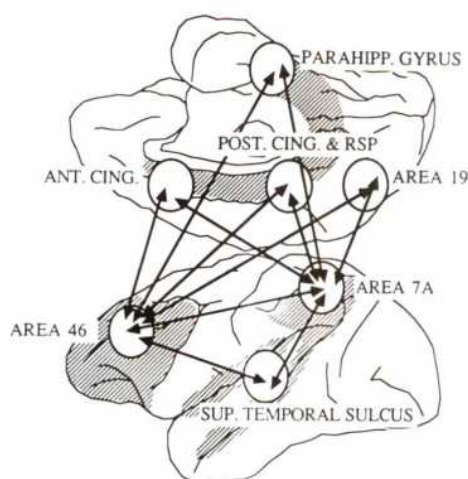


FIG. 2. Network of mutual reciprocal interconnections between frontal, parietal, temporal and limbic association areas. (Reproduced with permission from Goldman-Rakic, 1988a.)

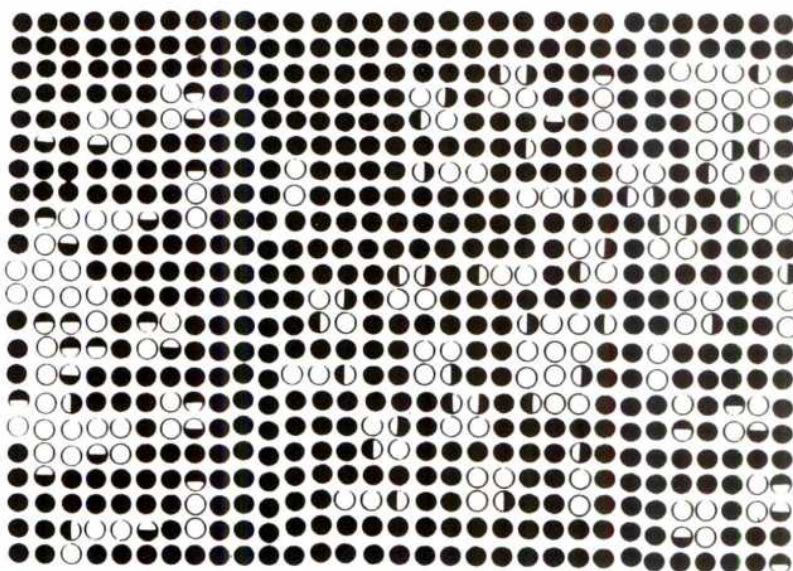


FIG. 3. Diagram of raster of cortical columns (as viewed from above) showing a pattern of distribution of excitation and inhibition. For further details, see text. (Reproduced with permission from Eccles, 1984.)

excited and the white ones inhibited, with the half-filled ones being moderately excited. By changing the distribution of black and white circles an entirely different, but equally unique pattern can be created capable of carrying a different informational content.

This strict column-to-column specific connectivity is counterbalanced by the presence of a profuse system of collaterals emanating from the efferent axons of pyramidal cells

which follow a more or less tangential course. They cover a radius of up to 3 mm and thus reach well beyond the confines of the column in which they originate. They make random connections with any apical or basal dendritic branch of other pyramidal cells which they encounter (Szentágothai, 1975, 1978). The lack of specificity of their connectional pattern contrasts with the highly specific pattern of columnar interconnectivity. These collaterals presumably allow information to break out from the relatively closed circuits made up by the quasi 'private' lines that interconnect specific columns.

It is within these interconnected neuronal nets showing an interesting mixture of specificity and nonspecificity of connections that distributed neuronal matrices carrying perceptual or mnemonic information are constructed. The simplest example of such a distributed neuronal matrix capable of carrying behaviourally significant information is that which represents specific smells in the olfactory system (Levetau and MacLeod, 1966; Mathews, 1972; Tanabe *et al.*, 1975; Takagi, 1986). It may serve as a simple model of how perceptual features or memories may be represented at a higher level of complexity in the cerebral isocortex. A review by Haberly and Bower (1989) has recently appeared which discusses in some detail the possibility of regarding the olfactory cortex as a model circuit of associative memory. Fig. 4 taken from Tanabe *et al.* (1975) shows how each specific odoriferous chemical elicits a widely distributed pattern of excitation and inhibition among a population of neurons in the olfactory cortex. A specific olfactory stimulus excites and inhibits many of these neurons; a different stimulus does likewise, but excitation and inhibition are distributed differently within the population of neurons, some of them participating in the response to both stimuli. Thus almost every cell responds to more than one odour, but there is no topographic representation of odours. The distributed matrix thus created within the population of olfactory neurons is specific for a given odour and differs from that elicited by another odour. It is thus the pattern of distribution of excitation and inhibition within the neuronal population

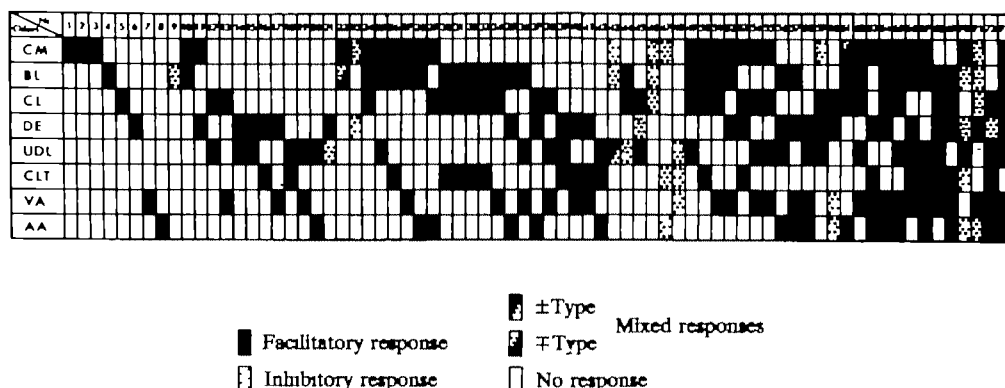


FIG. 4. Responses of 73 neurons (vertical columns) in the primary olfactory cortex of the monkey to 8 different odoriferous chemicals (horizontal rows). Black: excitation, stippled; inhibition of the neuron, white: no response. Only 9/73 cells responded to only one of the chemicals. (It is quite likely that had the list of the compounds used for testing been longer these cells may also have responded to more than one substance.) The cells are arranged from left to right in the order of the number of odoriferous chemicals to which they responded. Cell 73 responded to all tested substances except one. For further explanation, see text. (Reproduced with permission from Tanabe *et al.*, 1975.)

that represents a specific odour; no single cell by itself carries this information. Conversely, a single neuron can participate in a variety of matrices representing different smells.

The theoretical implications of the functioning of such networks has recently been worked out by several investigators (*see* monograph edited by Hinton and Anderson, 1981) and in particular by Rumelhart and McClelland (1986). The latter have developed the concept of parallel distributed processing as a fundamental principle in cognition. Fig. 5 illustrates a simple example taken from a chapter in their monograph

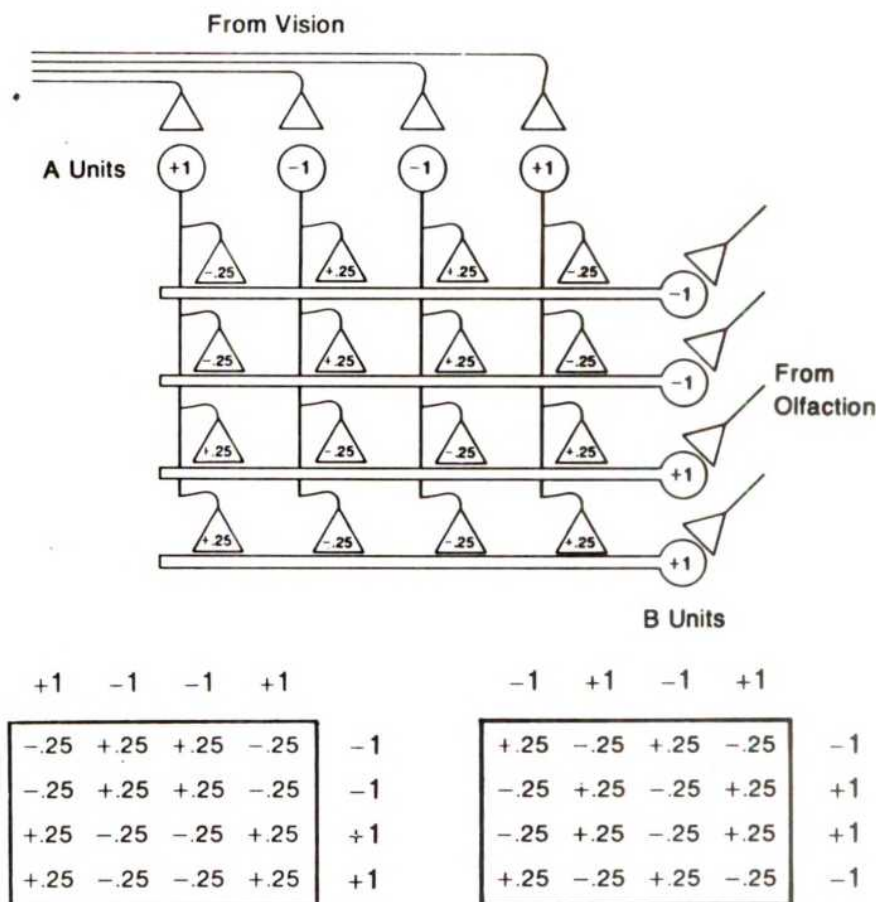


FIG. 5. *Upper.* A theoretical neuronal network functioning as a simple pattern associator. Patterns of activation in the A units can be produced by the visual system, those in the B units by the olfactory system. The synaptic connections allow the outputs of the A units to influence the activation of the B units. The synaptic weights linking the A to the B units were selected so as to allow the pattern of activation in the A units to reproduce the pattern of activation shown in the B units without the need of an olfactory input. If it is imagined that the synaptic weighting resulted from a previous association of the patterns shown in A and in B through a Hebbian mechanism of synaptic plasticity (association of visual with a simultaneous olfactory input), then a later occurrence of the visual input pattern shown here can reactivate the associated olfactory response configuration. *Lower.* Two matrices representing the associator of the upper panel showing different distributions of excitation. The pattern of distribution on the left represents the matrix created in the associator by the stimulus configuration shown in the upper diagram. For further details, *see* text. (Reproduced with permission from McClelland *et al.*, 1986.)

(McClelland *et al.*, 1986). It shows a simple network of units capable of parallel distributed processing. It consists of a matrix of 8 neurons, 4 receiving visual, 4 olfactory inputs. The synaptic connections between them carry different synaptic strengths which may have been shaped by experience. The lower left panel shows how within the population of these 8 neurons excitation (symbolized by a + sign) is distributed in response to a particular stimulus, say the sight and the smell of a rose; the panel on the right shows the distribution of excitation to a different stimulus, say the sight and smell of a steak. The two matrices differ, yet they share common units. Such a simple network has surprising properties that are of great heuristic value for the understanding of perception, learning and memory. It can be shown that exposure to the sight of a rose will create the distribution typical of the smell of a rose among the olfactory units. Such networks thus have powerful associative capabilities. A salient feature of this model is that patterns, of perceptions or memory, are not stored as such in the neuronal network. It is the strength of connections between neurons that allows these patterns to be created. An important attribute of such a system is that it can be activated as a whole by any of its constituent units, i.e., activation at one point within the network can recreate the whole pattern. This implies that recall can be initiated by any of the fragments making up the whole. Furthermore, the system tolerates a fair degree of degradation: units can be removed or noise can be introduced and the information is still maintained, although it becomes less precise. Another feature of such a system is that no unit 'represents' a specific item of 'memory' or 'perception', that is, the same population of neurons can participate in the representation of very disparate perceptions or memories. If the model is endowed with synaptic plasticity according to the Hebb rule (Hebb, 1949), specific connections within the system are strengthened through usage; it can learn.

We can now envisage how such a system could work in perception and memory as well as in memory recall. It also makes it possible to imagine how epileptic discharge or electrical stimulation of the temporal lobe, by acting through such a system, could induce experiential responses. I shall illustrate these points by using a pictorial metaphor. It is important that the metaphorical nature of this model be kept in mind; it must not be taken literally: its purpose is to illuminate in an easily accessible way some of the basic principles thought to be involved in the representation of experiences within the brain. It is a thought experiment using well-known methods of creating computer-generated pictures on a computer printout. Each character space as shown in fig. 6 represents a neuron. It can be either inactive or inhibited, in which case the space will remain empty, or it may exhibit different levels of excitation, as represented by printed characters. The number of dots forming the character and the superimposition of characters make it possible to create various shades of darkness which can be taken as symbolizing levels of activity displayed by a single neuron: the darker the character the higher the level of excitation of the neuron. Such computer printouts can be used to create pictures. Fig. 6 is actually the detail of such a picture; it is the area of the right eye of a complete image of the Mona Lisa, as shown in fig. 7A. In this computer-generated picture, each character space can be thought of as representing a neuron at the level of activation or inhibition necessary to create the matrix representing the Mona Lisa. Such a computer printout can be regarded as modelling a neuronal matrix representing not just the visual image of the Mona Lisa, but the experience of having seen or of remembering this work of art. It thus could incorporate, in addition to purely

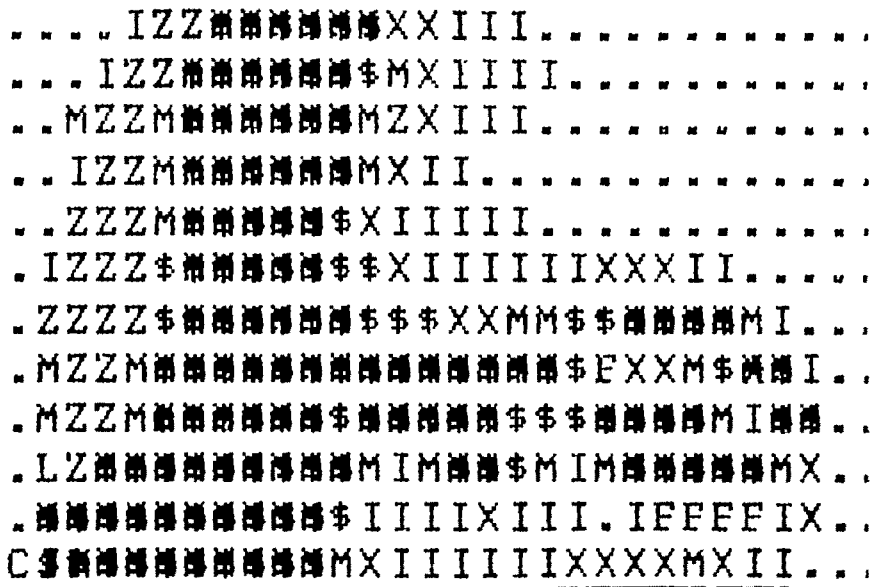


FIG. 6. Matrix representing different levels of excitation in a population of neurons as modelled on a computer printout. Each character space represents a neuron. The number of dots occupying such a space represents the level of excitation of the neuron: the more dots, the more excited the neuron. The number of dots depends on the character printed in that space and on the superimposition of characters. For further details, see text.

This modelling of the neuronal matrix, thought to be the substrate of a given experience as shown in fig. 7A is useful in demonstrating some of the properties of distributed neuronal networks. First, the experience is not in any way represented by the activity of any one of the single units that make up the whole matrix. This can be demonstrated by using the same population of units to represent an entirely different experience, such as that of the kid from *MAD* magazine shown in fig. 7B. These two representations differ from each other by the different pattern of distribution of excitation and inhibition within the same neuronal network, but both representations make use of the same neurons. Obviously, in spite of this, the two pictures derive from very different worlds of experience.

Another property of such networks is that they tolerate a great amount of degradation. A considerable number of elements that constitute the matrix can be inactivated, eliminated or destroyed at random and yet the representation remains recognizable. No single neuron

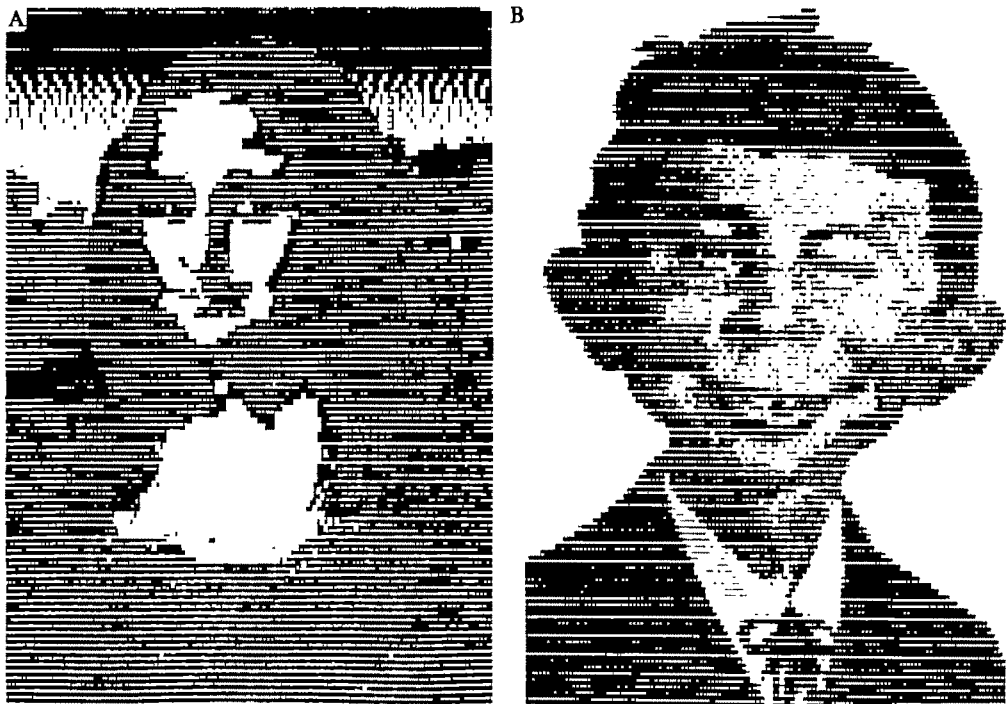
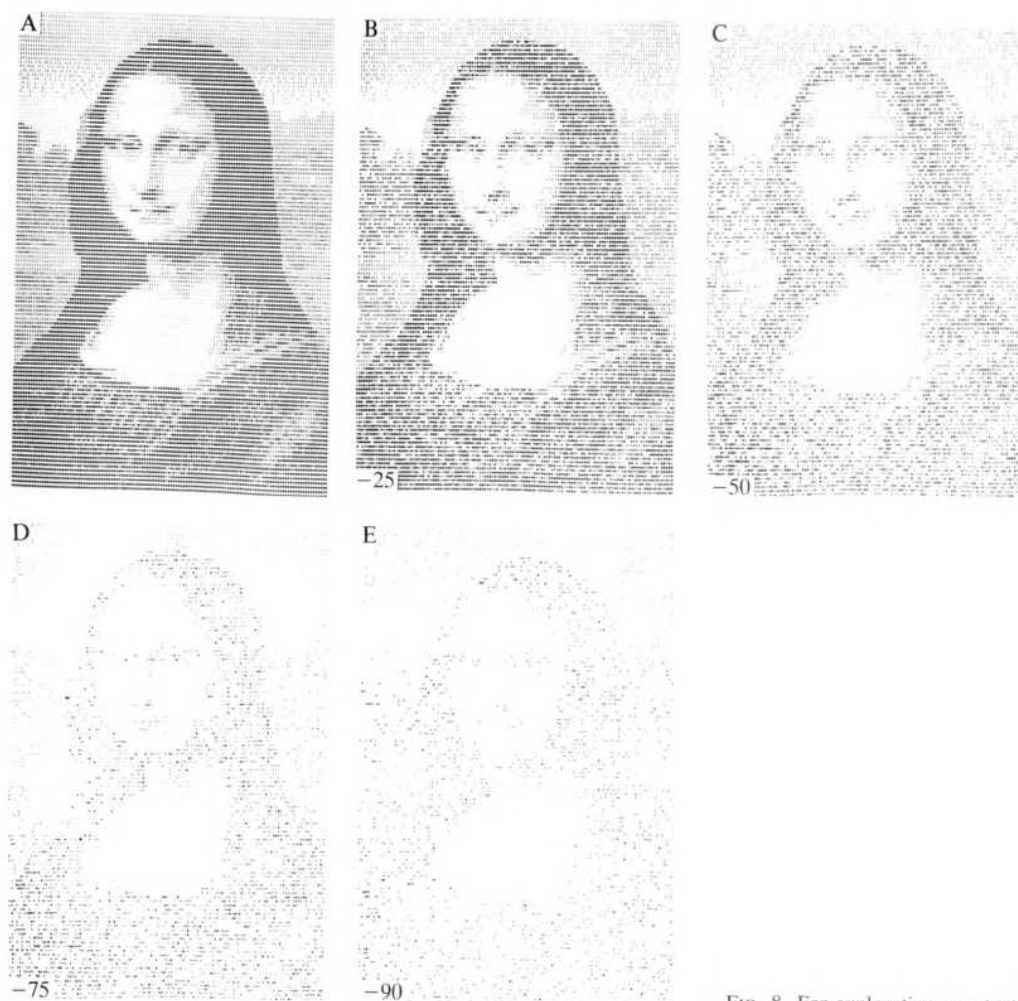


FIG. 7. For explanation, see text (B, with permission from *MAD* magazine)

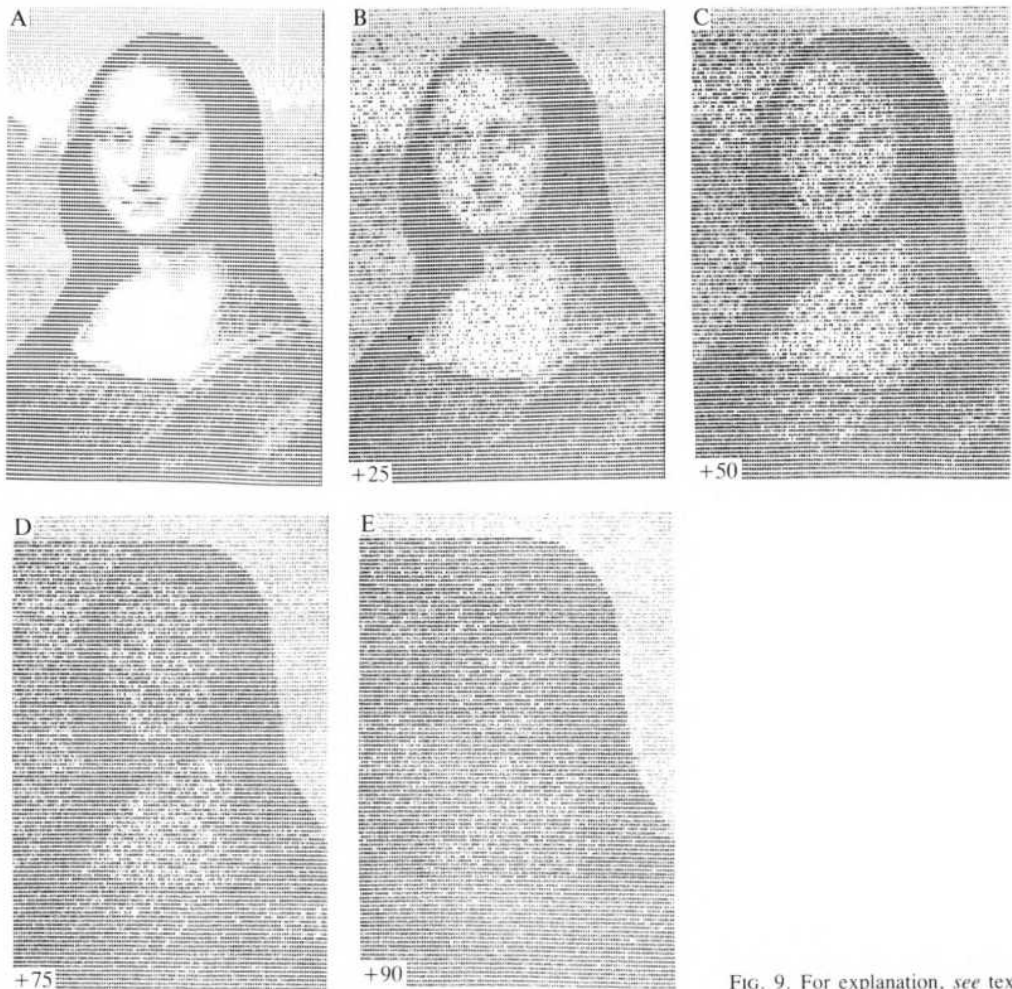
is thus essential for the representation of the experience. The sequence A to E of fig. 8 demonstrates this. In the computer-generated picture of the Mona Lisa, random removal of 25%, 50%, even of 75% of the characters still permits the computer to recreate a recognizable image although the picture becomes increasingly fuzzy and lacking in detail. The limit is reached at E when 90% is removed. Neuronal matrices probably have the same properties. Furthermore, according to Rumelhart and McClelland (1986) the rules governing networks capable of parallel distributed processing ensure that activation of any fragment of this network, because of the weighted strengths of the connections involved in creating the representation, is sufficient to recreate the whole picture. Thus to stay with the Mona Lisa metaphor, hearing the words 'Louvre' or 'Leonardo da Vinci' is likely to conjure up in our mind the experience of having seen the painting of the Mona Lisa.

Networks operating according to the rules of parallel distributed processing also tolerate a considerable amount of interference by noise. In a neuronal matrix, epileptic seizure discharge probably acts as noise. Thus if random noise is added, as shown in A to E of fig. 9, the picture again remains recognizable with the addition of 25%, 50% or even 75% noise; it becomes unrecognizable only in E when 90% noise is introduced. Again, there is increasing degradation of the quality of the picture and increasing lack of detail.

What does this model tell us about perception, memory, or more global experiences

FIG. 8. For explanation, *see text*.

under normal conditions, and about their reactivation through temporal lobe epileptic discharge or electrical stimulation of the temporal lobe? The first conclusion we can draw is that activation of only a subset of neurons involved in the representation of an experience, according to the properties of networks involved in parallel distributed processing, can recreate the full experience. We know that under normal circumstances a fragment of perception can serve as a stimulus triggering the full recall of an experience. In the case of experiential phenomena in temporal lobe epilepsy it is now possible to imagine that limited discharge in a group of neurons either in the amygdala or in temporal isocortex may utilize previously strengthened connections underlying an experience to recreate a widely distributed matrix of excitation and inhibition in a disseminated neuronal network within the brain that is the substrate of that particular experience. The tolerance for noise is even more interesting with regard to the possible underlying mechanisms of experiential phenomena in epilepsy. If indeed an epileptic discharge arising within

FIG. 9. For explanation, *see text*.

the temporal lobe is capable of recreating the matrix of a neuronal excitation in a distributed network that represents a given experience, the inevitable noise introduced by excessive discharge during a seizure may become capable of obliterating the experience only once the noise level has become quite high. Noise may also explain the fragmentary perceptual content of experiential hallucinations.

By utilizing current knowledge of neuronal connectivity both at the anatomical and functional level, it becomes possible to envisage the mechanisms through which epileptic discharge within the temporal lobe can activate the elaborate mental experiences that characterize the experiential phenomena of temporal lobe epilepsy. Furthermore, if these phenomena arise from the activation of matrices in distributed neuronal networks, then they could presumably be elicited from different locations within the temporal lobe, including temporal isocortex and various limbic structures. This permits the reconciliation of Penfield's observations (Mullan and Penfield, 1959; Penfield and Perot, 1963) which

emphasized the role of the temporal isocortex in the evocation of experiential phenomena, with those we have made (Gloor *et al.*, 1981, 1982) which stress the importance of limbic structures. The model would also accommodate the fact that experiences in temporal lobe seizures are fleeting and often fuzzy, since noise introduced by epileptic discharge may interfere with the expression of the underlying matrix and, as the intensity of discharge mounts, may ultimately render it unintelligible.

By applying modern insights into the neuroanatomy and neurophysiology of cortical and limbic interconnections on the one hand, and principles derived from modern concepts of cognitive science on the other, the study of experiential phenomena of temporal lobe epilepsy can illuminate our understanding of how the human brain may create human experience.

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THE ROLE OF DIENCEPHALIC PATHOLOGY IN HUMAN MEMORY DISORDER

EVIDENCE FROM A PENETRATING PARANASAL BRAIN INJURY

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SUMMARY

A patient (B.J.) is reported who developed severe memory impairment following a penetrating brain injury caused by a snooker cue which entered through his left nostril into the basal regions of the brain. Initially, his memory disorder had the clinical features of a dense amnesic syndrome, with both anterograde and retrograde amnesia, but B.J. subsequently showed significant recovery of memory function. Formal memory testing was carried out 21 months after injury. This demonstrated marked verbal memory impairment, as severe as that seen in patients with the amnesic syndrome. On nonverbal memory tests, his impairment was relatively mild and patchy. His retrograde amnesia had regressed mainly to affect a 6 month period before the injury. On other cognitive tasks, he performed at an average or above average level, and there was no neuropsychological evidence of frontal lobe dysfunction. Neuroradiological investigations at various stages after his injury failed to demonstrate a lesion in any of the thalamic nuclei. Magnetic resonance imaging showed a lesion in the hypothalamus in the region of the mamillary bodies. Our study demonstrates that marked, relatively focal, memory disorder after diencephalic injury can occur without direct pathology to the body of the thalamus. It also indicates that structures in or adjacent to the hypothalamus, such as the mamillary bodies, may play a more important role in human memory functioning than has hitherto been considered.

INTRODUCTION

There is continuing debate regarding the neuroanatomical basis of memory disorders. Structures within the medial temporal lobe and diencephalon have been the most favoured candidates for those which are critically related to human memory functioning. In the diencephalon, the thalamus has been the subject of a number of human and animal investigations concerned with learning, and a wide variety of cerebral pathologies have implicated the thalamus as being important for mediating mnemonic processes (Kapur, 1988). One of the most notable case studies in this respect has been that of patient N.A. (Teuber *et al.*, 1968), who incurred a penetrating paranasal missile wound caused by a miniature fencing foil. On the basis of CT scan evidence (Squire and Moore, 1979), it was thought that the main underlying pathology was in the region of the left dorsomedial nucleus of the thalamus. Subsequent studies using magnetic resonance imaging (Squire *et al.*, 1989) have indicated more widespread pathology, including lesions in the left thalamus, left mamillothalamic tract, mamillary bodies, the hypothalamus and right

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anterior temporal lobe. There is some uncertainty as to the role of the thalamic pathology in the mediation of N.A.'s memory disorder (Weiskrantz, 1985; Zola-Morgan and Squire, 1985), and the more recent imaging data would appear to highlight the possible role of other diencephalic structures in this patient's memory difficulties. There is also evidence that pathology in structures other than the thalamus or hippocampus, such as damage to the basal forebrain, may result in marked memory disorder (Phillips *et al.*, 1987).

In the present case study, we examined the role of diencephalic pathology in human memory functioning by the investigation of a patient who sustained a penetrating head injury similar to that suffered by N.A. Our patient, B.J., received an injury in which a snooker cue entered his brain through his left nostril. He was initially left with a dense amnesic state, and at 21 months postinjury we had the opportunity to assess his cognitive function in detail. A detailed clinical report of our patient's injury and the resulting hypopituitarism has been presented elsewhere (Rawlinson *et al.*, 1988).

CASE REPORT

Case history

B.J., a right-handed food production manager (d.o.b. January 3, 1959), left school at the age of 17 yrs. He subsequently obtained 7 'O' level passes, and 2 diplomas in food technology. His past medical history is unremarkable apart from some evidence of excessive alcohol consumption in the recent past; during the 2 yrs before his injury, he had a heavy consumption of alcohol, but prior to this his alcohol intake had mainly been social. There was no evidence of any adverse effects of his alcohol consumption on his general health or on his work efficiency, and it is unlikely that his alcohol consumption had any major or permanent effect on his cerebral function. Since his injury, he has totally abstained from alcohol.

B.J. was 27 yrs old when he sustained a penetrating head injury on October 4, 1986, this injury taking place in England. During a game of snooker, a brawl developed and in the ensuing disturbance a snooker cue was pushed up his left nostril. He was admitted to a district general hospital, at which time he was reported as being somewhat inebriated and uncooperative. Over the next 24 h he developed symptoms of meningitis with pyrexia and neck stiffness. His level of consciousness deteriorated, and he was then transferred to a neurosurgical unit. On arrival at this unit, he complained of headache, irritability and photophobia. At this stage, he was conscious but drowsy with some pyrexia. A skull x-ray showed some subarachnoid air and it was thought that the snooker cue went through the left ethmoid cells into the floor of the anterior fossa. A CT scan was interpreted as showing several bubbles of air in the lateral ventricles and around the brainstem. A further air shadow was visible just in front of the anterior clinoid process. B.J. was given antibiotics and his initial clinical progress was considered to be satisfactory. His pyrexia and neck stiffness resolved within a few days, and at this stage there was no evidence of a CSF leak. A repeat skull x-ray on October 14, 1986 showed opaque left ethmoid cells and features suggesting a fracture of the anterior fossa floor. On October 15, he became increasingly drowsy and developed a further pyrexia, although without neck stiffness. A repeat CT scan showed haemorrhage in the interpenduncular cistern, and evidence that damage was more posterior than the cribriform plate and might involve the pituitary gland. Hormone profile studies showed depressed anterior pituitary function. Cortisone replacement therapy was initiated and his condition then improved. Several days later a CSF leak occurred from B.J.'s left nostril, and sagittal tomograms showed a fracture of the anterior wall of the pituitary fossa. On October 24, a transnasal exploration of the right nostril indicated a circular defect in the posterior wall of the sphenoid air sinus. The pituitary fossa contained a horizontal fragment of bone which appeared to transect the pituitary stalk. A fascia lata skin flap was placed over the skull defect. Postoperatively, there was only a minor, occasional CSF leak which cleared within a few days. No specific neuropsychological investigations were carried out at this stage, although it was observed that B.J. was 'confused' with no memory of the injury or of the following days. At this stage, there were no firm signs of diabetes insipidus, although he showed some polyuria and polydipsia in the fourth week of his hospital stay.

On November 7, B.J. was transferred to the Royal Victoria Hospital, Belfast. A CSF leak was noted at the time of admission, but the major abnormality which he was observed to display was a dense amnesic

state. A number of investigations were performed. Ophthalmological assessment was normal, but endocrine investigation revealed hypopituitarism. Further CT scans, including some with an intrathecal contrast medium, showed leakage into the sphenoid sinus. CT scans at this stage and at later stages of his recovery, some of which included 4 mm cuts, failed to detect evidence of a lesion in any part of the thalamus. A further surgical procedure to repair the CSF leak was performed; 24 h postoperatively, he developed meningitis which responded to antibiotic treatment. Over the next few weeks there was some evidence of polyuria from diabetes insipidus, but his major deficit remained that of a marked memory disorder. B.J. was discharged home on December 12, 1986.

On a number of outpatient appointments over the next 18 months his amnesia was observed to show some recovery, but his marked memory disorder remained clinically obvious. He also had significantly increased appetite and had reported loss of libido. His wife had indicated that he was much more short-tempered and verbally aggressive than before his injury. From the endocrine standpoint, he was treated with DDAVP, with cortisone replacement therapy, and with testosterone.

In August 1989, B.J. underwent magnetic resonance (MR) imaging of the brain. MR images were acquired on a 1.5 Tesla scanner (Siemens Magnetom) in the axial, coronal and sagittal planes, with thin slices through the region of the mamillary bodies. The mamillary bodies could not be identified on the sagittal images (fig. 1A) and on the coronal scans they appeared small and atrophic (fig. 1B). No abnormality was seen in the temporal lobes, hippocampus or thalamus.

Neuropsychological investigations

B.J. was seen for detailed neuropsychological testing in June and July 1988. On questioning, he had a pretraumatic amnesia (i.e., memory loss for events in the period immediately preceding the injury) of several months' duration, although this was somewhat patchy. He had no recollection of the injury or the days preceding it. He had been living in England for 10 wks before his injury and could only recall isolated items from this period. For example, he could picture the outside of the hotel in which he was staying, a facial feature of the hotel owner, and the dining room of the hotel, but he could not picture his own bedroom in the hotel nor could he recall any other part of his stay. He could picture in his mind the front of the factory in which he worked and the general work area, and he could give the names of the key personnel in the factory. However, he could not picture the office in which he worked and admitted that his overall memory for the 10 wk period of employment was poor. He could not recall his journey from Northern Ireland to England, nor his first day at work with his firm in England. His memory for his previous 2 yrs employment in Northern Ireland was patchy, although better than for the 10 wks spent in England. He was unable to recall his last day of work with the firm for which he worked before going to England, although he could recall his first day there. His immediate pretraumatic amnesia appeared to merge into a more general and somewhat patchy retrograde amnesia. More detailed information on the latter is presented later.

With respect to B.J.'s posttraumatic amnesia, he was unable to recall any of the 4 wk hospital stay in England or travelling by air back to Northern Ireland. His wife indicated that when she visited him in England in the first few days after the injury, he was able to recognize her and his children but claimed that they were not married. He also told the nurses in the ward that he was not married, but he often asked about his son (then 2 yrs old) by name. The first postinjury memory that he was able to offer was a brief memory of his wife admonishing him at the airport in Northern Ireland after they had arrived there from England. He had little recollection of his 5 wk stay in the Royal Victoria Hospital, Belfast. His posttraumatic amnesia appeared to be particularly dense for the 3 month period after the injury, although his memory for subsequent events is of course impaired because of his persistent anterograde memory disorder.

At the time of the assessment, B.J. was very much aware of his memory difficulties. He was also aware of increased irritability since the injury and of loss of sexual drive, although there was no evidence of impotence as such. He had also been aware of impairment in his sense of smell since the injury. His wife thought that his memory was still significantly impaired, and thought that the improvement which had occurred after the injury had largely plateaued in the previous 5–6 wks. She commented on his increased irritability since the injury, and did not think that he had any other symptoms. In particular, she did not think he had any impairment in speech.

At the time of the assessment, B.J. was attending a day centre, and he was managing to do quite complex woodwork which he himself was designing. Although his everyday memory function is noticeably impaired,

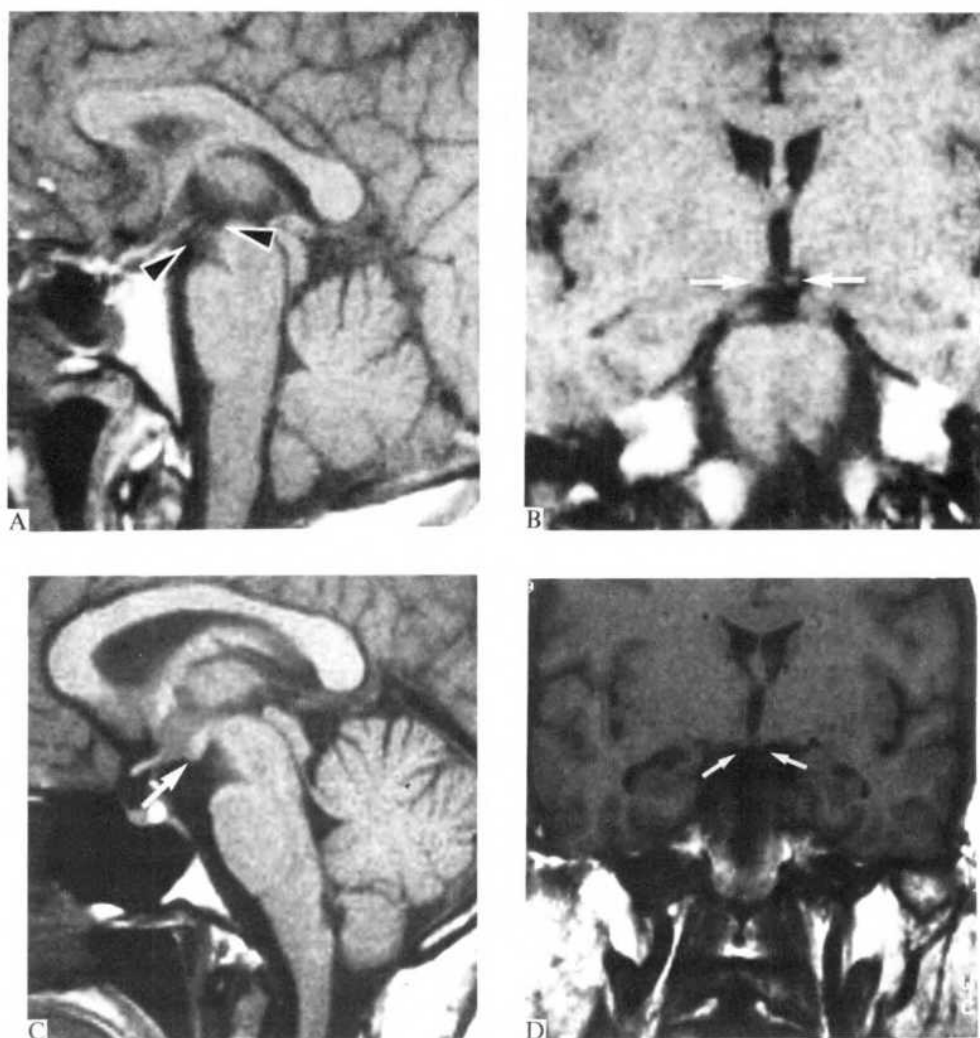


FIG. 1. Sagittal SE 500/17 (A) and coronal SE 500/28 (B) MR scans through the region of the mamillary bodies. Slice thickness is 4 mm in A and 5 mm in B. On the sagittal scan, there is downward bulging of the third ventricular floor, and absence of the normal impression of the mamillary bodies (arrowheads). On the coronal scan, the mamillary bodies appear small and atrophic (arrows). Normal sagittal (C) and coronal (D) views of the mamillary bodies (arrowed) for comparison.

he has been able to retain some information, especially for major events or information which has been repeated a large number of times. Thus, for example, he has been able to learn one of our names (H.D.) on the basis of a number of interactions over the past year, and he was able to describe a short holiday on which he had been since the injury.

General cognitive functioning. B.J. was administered the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955). For practical reasons it was not possible to administer the revised scale, but in view of his high scores it is unlikely that this would have yielded significantly different results. He obtained

a Verbal IQ of 128, a Performance IQ of 114, and a Full Scale IQ of 123. The latter IQ score is higher than his predicted premorbid IQ (105) on the basis of an adult reading test (Nelson, 1982). His WAIS subtest scores are indicated in Table 1. On a modified version of the Wisconsin Card Sorting Task (Nelson, 1976), he was able to sort by all 6 categories. On the verbal fluency subtest of the Minnesota Aphasia Examination (Benton and Hamsber, 1978), he did not have any impairment, performing at the 77th percentile.

TABLE 1 BJ's PERFORMANCE ON THE WECHSLER ADULT INTELLIGENCE SCALE

	<i>Verbal IQ</i>	<i>Performance IQ</i>	<i>Full scale IQ</i>	<i>Subtest scores (age-scaled)</i>
WAIS	128	114	123	Information—12 Comprehension—17 Arithmetic—15 Similarities—15 Digit Span—16 Vocabulary—13 Digit Symbol—10 Block Design—17 Picture Arrangement—9 Picture Completion—13 Object Assembly—11

Anterograde memory functioning. B.J. was administered the Rivermead Behavioural Memory Test (Wilson *et al.*, 1985), the Wechsler Memory Scale—Revised (Wechsler, 1987), a recognition memory test for words and faces (Warrington, 1984), the Rey Auditory Verbal Learning Test (Lezak, 1983), and verbal and nonverbal learning tasks (Coughlan and Hollows, 1985). Most of this testing was undertaken in June or July 1988, with the exception of the latter learning tasks and the recognition memory assessment, which were performed in August 1989. His scores on the first 3 of these tests are given in Table 2. On the Rivermead Behavioural Memory Test, his overall screening score of 2/12 is in the severely impaired range. The 2 items on which he performed successfully related to recognition of pictures and recognition of faces. For the Wechsler Memory Scale, he performed particularly poorly on delayed memory testing. His faces

TABLE 2 BJ's MEMORY TEST PERFORMANCE

<i>Test</i>	<i>Scaled score</i>
Wechsler Memory Scale—Revised	
Orientation	11/14
General Memory	80
Verbal Memory	78
Visual Memory	91
Attention/Concentration	130
Delayed Recall	54
Logical Memory (Immediate)	35 percentile
Visual Reproduction (Immediate)	96 percentile
Logical Memory (Delayed)	1 percentile
Visual Reproduction (Delayed)	16 percentile
Rivermead Behavioural Memory Test	
Screening score	2
Recognition Memory Test	
Faces recognition	12
Words recognition	7

recognition memory scores were above average for faces, and in the low average range for words. His performance on the Rey Auditory Verbal Learning Test was markedly impaired, particularly on the delayed recall component. His performance on this test, together with that of a group ($n = 20$) of matched control subjects, is shown in fig. 2. Although his recognition memory score was similar to the maximum score obtained by control subjects, he made many more false positive responses—4 compared with a mean of 0.3 for control subjects.

B.J.'s performance on learning tests involving word list material and visual designs respectively is shown in fig. 3. On the word list learning test, his performance over the 5 learning trials and also the delayed

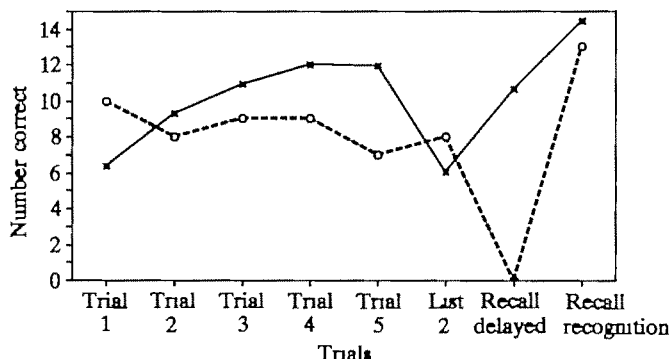


FIG. 2. Performance of B.J. and control subjects on the Rey Auditory Verbal Learning Test. Continuous line = controls; dashed line = B.J.

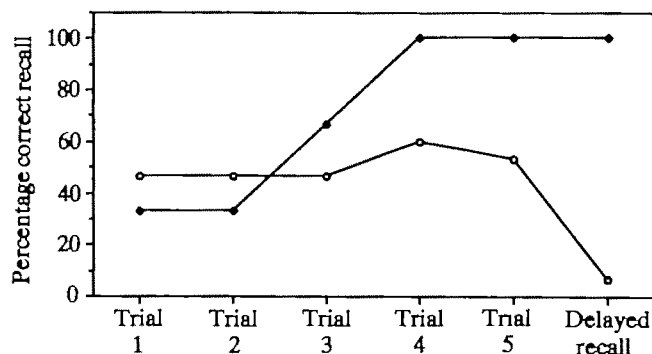


FIG. 3. Performance of B.J. on a word list (open circles) and a design learning test (filled diamonds) (Coughlan and Hollows, 1985) over 5 trials and on a delayed recall trial administered after an interpolated learning trial.

recall trial was well below the 10th percentile. On the design learning test, his score on the initial learning trials was only slightly below average (10–25th percentile), and on the delayed retention trial his score was normal (50th percentile).

In summary, B.J. showed a marked verbal memory deficit, as severe as that found in patients with the amnesic syndrome, whereas his nonverbal memory performance was generally normal or relatively mildly impaired.

Remote memory functioning. B.J.'s autobiographical memory was assessed by means of a structured interview covering past personal events. The particular items selected for this interview were based on

an initial interview with his wife, and covered the following areas: educational experience, hospital treatment, holidays, occupational history, houses in which he had lived, births and deaths in his family, and his own elopement and marriage.

On the basis of this interview with B.J., there was no evidence of any significant retrograde amnesia other than the patchy loss for some months before the injury as described earlier. The items which he failed to recollect at the time of the neuropsychological assessment mainly referred to his inability to date particular episodes accurately, such as the birth of one of his children in 1985, the dates when he lived at certain addresses, etc. He gave the year of his marriage as 1982 rather than the true year of 1981, but gave the correct month and date. Other past memory difficulties included his failure to have other than a vague recollection of being at the birth of his son in 1982, and his inability to recall being at the birth of his daughter in 1985, which took place 18 months before his injury. He indicated that after his injury he had completely to relearn to use his scientific calculator which he could use proficiently before his injury. Apart from these memory difficulties, he could give an accurate account of past events relating to the various categories outlined above. He could recall specific incidents which occurred several years before his injury, and was able to describe an incident about a year before his injury when one of the pipes burst in his house and resulted in the ceiling collapsing. The fact that he could not recall his last day of work in Northern Ireland or his first day of work in England, but could recall some incidents from his 2 yr employment period before going to England, would appear to suggest a significant retrograde amnesia of 6 months, with only isolated memory failures for events before this. Even the 6 month period of pretraumatic amnesia was not absolute, for example, he could picture the landlady of the hotel in which he was staying in the months before his injury, and he could remember a few details of the place in which he was working around this time. Both he and his wife were aware of a considerable degree of shrinkage in his retrograde amnesia over the previous year, although we have no formal evidence to document this change objectively.

B.J. was also administered 2 tests of past public events, one relating to memory for famous scenes (Kopelman, 1989) and the other test, the Dead-or-Alive test (Kapur, unpublished), relating to memory for famous personalities. In the famous scenes test, he was shown 10 scenes relating to well-known events which had occurred between 1975 and 1984 (earlier items were also administered but not scored, as they referred to events when he would have been aged less than 16 yrs). He was asked to indicate what the scene depicted and was also administered a forced-choice recognition test for each item. He was further asked to date the event and was required to choose from a set of 10 5-yr time periods. Fig. 4 shows that B.J. was largely unimpaired on this task as compared with the performance of a group of 3 control subjects matched for age and educational level (mean age 32 yrs; mean age-scaled score on WAIS Information subtest = 11.7). His score on the dating component was slightly lower than that of controls, although this part of the task is also difficult for some control subjects, and B.J.'s performance may simply reflect chance variability in this respect.

In the Dead-or-Alive test, B.J. was shown the name of a personality and asked to indicate whether the person was alive or dead, how they died (killed or of natural causes), and when they died. Forty names in all were presented, 10 of living personalities and 30 for personalities who had died since 1960. For

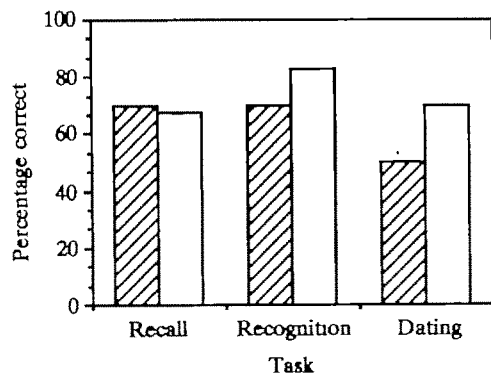


FIG. 4 Performance of B.J. and control subjects on identification of famous scenes. Hatched areas = B.J.; open areas = controls

these 30 personalities, 10 items covered each of the 3 decades since 1960, and 4 items within each set of 10 referred to a personality who was killed. To allow for B.J.'s age and time of injury, we excluded 2 items from the 1980s which related to personalities who died in 1987, the year after he incurred his injury, and also excluded items earlier than 1970. His scores for items from the 1970s and 1980s, together with that of control subjects, are given in fig. 5. This shows that he exhibited no significant impairment, and his pattern of scores—better performance on items from the 1980s than the 1970s—is the reverse of that which is generally found in amnesic patients with a notable degree of retrograde amnesia.

In summary, B.J. showed little evidence of the dense retrograde amnesia that is seen in certain amnesic patients such as those with Korsakoff's syndrome. We would consider that his retrograde amnesia mainly covers a 6 month period before his injury, with relatively minor memory loss for events earlier than this.

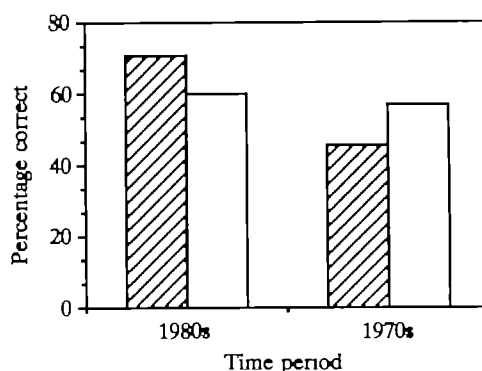


FIG. 5 Performance of B.J. and control subjects on 'Dead-or-Alive' test. Hatched areas = B.J.; open areas = controls

DISCUSSION

As a result of a penetrating paranasal head injury, our patient B.J. demonstrated a relatively focal memory disorder which was characterized by marked verbal memory impairment. Nonverbal memory functions were much less impaired, with normal performance or only mild impairment on a number of nonverbal memory tasks. Pretraumatic amnesia in our patient merged into a more general retrograde amnesia, but this was limited to about a 6 month period before his injury, with isolated episodes of memory failure for events prior to this period. CT scanning provided some evidence to suggest a lesion in basal regions of the brain, although none for a lesion in the thalamus. MRI showed a lesion in the area of the mamillary bodies.

The injury which B.J. displayed bore a number of similarities to the fencing foil injury sustained by the noted patient N.A. (Teuber *et al.*, 1968). In both cases, a lesion in the basal regions of the brain was caused by a penetrating injury through the nasal cavity. It is, however, worth pointing out a few differences in clinical features between the 2 cases. In N.A., a fencing foil entered the right nostril and went across the midline towards the region of the left thalamus. In our patient, the snooker cue entered the left nostril and went directly into the left side of the hypothalamus. We were not able to locate the particular snooker cue used to inflict the injury, but it was probably much wider than the fencing foil, thought to be around 2 mm in diameter, which caused N.A.'s lesion (B.J.'s skull defect caused by the entry of the snooker cue was around 5 mm in diameter). It is also possible that the velocity of the missiles in the 2 cases was different,

but again we do not have any firm evidence of this. At the clinical level, there are also several differences between the 2 cases. N.A. displayed paralysis of upward gaze as a result of his lesion, and this has persisted to some degree since the injury. Whether this is due to damage to the posterior commissure, as Weiskrantz (1985) has argued, or results from thalamic pathology, remains uncertain. B.J. has clinical and radiological evidence of damage to the pituitary region of the brain and some clinical evidence of hypothalamic dysfunction. By contrast, N.A. has never shown any clinical evidence of damage to the pituitary gland and, conversely, B.J. has never shown any evidence of vertical gaze paralysis. This clinical evidence would tend to point towards a more anterior and ventral focus for the primary brain injury in B.J., and a more posterior and dorsal locus in N.A.

B.J.'s pattern of memory disorder was strikingly similar to that shown by N.A., although we have obviously not been able to administer the full range of memory tasks which N.A. has performed over the years since his injury in 1960, and a number of tests which we gave to B.J. have only been developed and published in the past few years. The focal verbal memory deficit which B.J. displayed is as severe as that found in patients with the amnesic syndrome, and contrasts with the normal or mildly impaired scores on corresponding nonverbal memory tasks. The absence of any additional cognitive dysfunction, in particular the lack of evidence suggesting frontal lobe pathology, is again similar to the picture in N.A. This feature, together with B.J.'s insight and concern about his memory difficulties, contrasts with the clinical picture shown by many patients with Korsakoff's syndrome whose memory performance and absence of subjective awareness of their memory difficulties are similar to what is found in some patients with frontal lobe pathology. B.J.'s relatively limited retrograde amnesia is again similar to the remote memory performance of N.A., who has consistently performed well in this aspect of his memory functioning. As was true for anterograde memory function, this pattern of performance contrasts with that resulting from other causes such as in Korsakoff's syndrome. It highlights the dissociations which can occur between anterograde and retrograde memory function (Shimamura and Squire, 1986) and suggests that different and/or more extensive pathology may underlie cases of marked remote memory loss. Our data, and those from the patient N.A., on the pattern of anterograde and retrograde memory performance, raises the possibility that having a relatively preserved nonverbal memory may provide a sufficient basis for reconstructing remote memories.

None of the CT scan examinations carried out after B.J.'s injury, nor the MR scan, showed any abnormality in the body of the thalamus. In this respect, he differs significantly from the patient N.A., whose initial CT scan showed a lesion in the left dorsomedial nucleus of the thalamus and whose subsequent MR scan demonstrated additional diencephalic pathology together with a small lesion in the right anterior temporal lobe. Some of B.J.'s CT and MR images were at 4 mm intervals, and it is likely that if a small thalamic lesion had been present it would have been visible on at least one or more of the cuts. On the basis of our knowledge of the injury which he sustained, and the probable track of the snooker cue as it entered the brain, we consider that the most likely structures to have been damaged were the hypothalamus, including the mamillary bodies and possibly also the mamillothalamic tract. We consider that the body of the thalamus is too high to have been damaged directly by the injury, and that the

fornix is also too high to have been severed. Our imaging data point to a lesion in the posterior hypothalamus, with probable involvement of one or both mamillary bodies. Some of the earlier published reports of memory disturbance after hypothalamic damage have been based on patients with cerebral tumours (e.g., Reeves and Plum, 1969; Beal *et al.*, 1981; Berkovic *et al.*, 1988); it is quite possible that in such patients the mamillary bodies were damaged by the lesion—1 of the patients in the series reported by Berkovic *et al.* (1988) appeared to have pathology centred around the right mamillary body, although it seems that there may also have been more general displacement of structures adjacent to the third ventricle. This patient was reported to have marked memory difficulties as part of his clinical condition. A recent clinicopathological study (Flynn *et al.*, 1988) of a patient who underwent surgical removal of a craniopharyngioma showed clinical features quite similar to those present in B.J.—marked memory disturbance, hyperphagia with obesity and episodic rage. Although detailed memory testing was not reported, there appeared to be no significant retrograde amnesia, as was also true for B.J. Neuropathological investigations highlighted damage to the ventromedial hypothalamus, and while this is adjacent to the mamillary bodies, no specific reference was made by Flynn *et al.* to the integrity of these latter structures. Two earlier reports of patients with amnesia following penetrating head injury have provided radiological evidence of hypothalamic/mamillary body injury (Czechmanek, 1954; Jarho, 1973), although both of these investigations, and also the studies by Teuber (1969) which implicated third ventricle structures in profound disturbances of memory, were carried out before the introduction of computerized tomography. Data from animal studies (e.g., Zola-Morgan *et al.*, 1987) have indicated that focal mamillary body lesions alone do not result in significant memory impairment, although there is considerable evidence from human studies which implicates the mamillary bodies in human memory disorder (e.g., Mair *et al.*, 1979; Charness and DeLaPaz, 1987; Mayes *et al.*, 1988). It remains an open question as to whether the critical lesion in B.J. affected connecting pathways such as the mamillothalamic tract rather than the mamillary bodies themselves, since this tract is generally considered too small to be easily visualized with current imaging technology. A hypothesis supporting the role of the mamillothalamic tract in B.J.'s memory disorder would be consistent with other evidence (von Cramon *et al.*, 1985) which has emphasized the importance of this tract in the mediation of human memory function.

Our findings cannot readily be reconciled with hypotheses which propose that amnesia is caused by conjoint lesions of circuits involving only the hippocampus and the amygdala. In the case of B.J.'s lesion, it is possible that some of the afferent connections from such structures in the medial temporal region to the hypothalamus or to structures adjacent to the hypothalamus may have been directly or indirectly damaged by the injury, for example, the projections from the amygdala to the hypothalamus via the stria terminalis or via the amygdalofugal pathway, or the projection from the hippocampus via the fornix to the mamillary bodies. In our patient both of these target structures may have been damaged, and our anatomical data would then be consistent with the evidence reviewed by Mishkin and Appenzeller (1987), where damage to diencephalic targets of medial temporal projections resulted in amnesia. Thus we would agree with their conclusions that 'the diencephalon and the limbic structures participate in a circuit rather than making totally independent contributions to memory' (p. 85).

We consider that the hypothalamic damage sustained by B.J. may also have been responsible for the marked change in temperament and changes in appetite control which he suffered. Such changes have been reported in some patients with known hypothalamic pathology (e.g., Reeves and Plum, 1969). The precise mechanisms underlying such disturbances remain to be clarified, though it is possible that projections which exist from frontal cortex to the hypothalamus become disrupted in some way by a lesion in certain nuclei of the hypothalamus itself, and that such indirect frontal lobe pathology suffered by B.J. may have contributed to these changes.

Our findings do not necessarily negate the significance of the thalamic lesion found in the patient N.A. It is quite possible that this lesion occurred as a direct result of his injury, and that it plays an important role in his memory disturbance. Our results do, however, point to the conclusion that this lesion is not necessary for a memory disturbance to result after damage from such a penetrating brain injury. Our observations, together with the recent imaging data on the patient N.A., highlight the possible role of the hypothalamus and in particular the mamillary bodies, with their afferent/efferent connections to medial temporal structures and other parts of the diencephalon, in mediating human memory functioning. However, detailed confirmation of neuroanatomical conclusions reached by MR studies such as our own must await histopathological analyses of postmortem material, and any hypotheses should remain tentative until such evidence becomes available.

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NEURONAL ACTIVITY IN THE MEDIAL GENICULATE NUCLEUS AND IN THE AUDITORY CORTEX OF THE RHESUS MONKEY REFLECTS SIGNAL ANTICIPATION

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SUMMARY

A Rhesus monkey was trained to discriminate between 2 acoustic signals, preceded by visual cues, that instructed which of 2 movements to make. In 75% of the trials the visual cue correctly indicated which of the 2 acoustic signals would follow. In 25% of the trials the visual cue was misleading, readying for the wrong acoustic signal. Based on the visual cue the monkey could anticipate which acoustic signal would be presented, a possibility confirmed by behavioural analysis. Movements conforming with the acoustic instruction signals were reinforced. The activity of 65 medial geniculate nucleus (MGN) and 107 primary auditory cortex (ACx) neurons was recorded during task performance. Significant response differences to anticipated vs unanticipated acoustic signals were found in 32% of the MGN and 27% of the ACx neurons. In both structures some of the affected neurons responded more vigorously to the correctly anticipated acoustic signals while others responded more vigorously to the unanticipated ones.

An index of relative response intensity (RRI) was derived for each neuron by comparing its response to the sound signal in reinforced trials with that obtained in trials with no visual cues and no reinforcement (a 'blank' condition). For both MGN and ACx the analysis of RRIs revealed two anticipation-related effects. One consisted of response facilitation to anticipated sound signals together with suppression of responses to unanticipated sound signals. The other consisted of facilitation of responses to unanticipated sound signals, combined with base-line responsiveness to anticipated sounds. These effects can be interpreted to reflect a context-relevant trial by trial selection of neuronal channels which conduct information along the thalamo-cortical segment of the auditory system. The similarity between the effects of anticipation at the thalamic and the cortical levels suggests that the changes in excitability which underlay trial by trial neuronal selectivity occur subcortically.

INTRODUCTION

In a previous study we found that the response of some auditory cortex (ACx) neurons to sound stimuli depended on whether the type of these sounds was anticipated. We suggested that the anticipation of acoustic signals involves two neural mechanisms which together compare the actual signal with its anticipated image (Hocherman *et al.*, 1981a). An involvement of subcortical structures in this process was suggested by the short latencies of the affected responses. To test this possibility we sought to look for anticipation-related effects in the medial geniculate nucleus (MGN), using the same experimental procedures which were employed in our previous investigation of the cortex. To facilitate a comparison between the effects of anticipation at both CNS levels we

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recorded the activity of primary ACx neurons in the same animal in which the MGN recordings were made. The MGN provides the main input to the ACx and much is known about its connections and morphological subdivisions (Aitkin and Webster, 1971; Jordan, 1973; Mesulam and Pandya, 1973; Allon *et al.*, 1981). The basic encoding properties of its main component, the parvocellular portion, are well documented (Aitkin and Webster, 1972; Phillips and Irvine, 1979; Calford and Webster, 1981); however, the role of the MGN in mediation of behaviour is still unclear. A few studies showed an increase in the response of MGN neurons to classically conditioned acoustic signals (Gabriel *et al.*, 1975; Gilat and Perlman, 1984). Other investigators were unable to obtain comparable results, or find behavioural modulation of neuronal activity outside the magnocellular subdivision (Ryugo and Weinberger, 1978; Birt and Olds, 1981; Gonzalez-Lima and Scheich, 1984). Similar disagreement applies to the inferior colliculus (IC), which provides most of the afferent input to the MGN. Behaviourally-related response changes in the principal part of the IC were reported by some investigators (Ryan and Miller, 1977; Gonzalez-Lima and Scheich, 1984), but not by others (Birt and Olds, 1981). These conflicting findings seem to arise, at least in part, from methodological differences between various studies.

The present study attempted to determine whether the MGN is involved in anticipation-related processing of auditory information. The nature of this information, rather than its timing, was made the subject for anticipation, as in our previous study.

METHODS

Behavioural task

The task used was designed to make monkeys anticipate the occurrence of 1 out of 2 possible acoustic signals. This was accomplished by the combined use of two types of trials: discrimination and blank trials. In the discrimination trials, a 0.1 s flash of light was followed, after a 0.4 or 0.8 s interstimulus interval (ISI), by a 0.1 s sound signal. The monkey could gain a 0.1 ml of fruit juice reward by moving a lever, within 0.1 s to 0.6 s after termination of the sound signal, in a direction indicated by it. The flash of light could come either from the right, usually followed by a pure tone, or from the left, usually followed by a burst of white noise. The monkey had to move the lever to the right after a tone and to the left after a noise signal. Moving the lever at a time other than the allowed response interval resulted in abortion of that trial and in delay of the next one. In about 75% of the discrimination trials the normal sequence, tone after a flash from the right or noise after a flash from the left was observed. In about 25% of the trials the light-sound sequence was misleading in that the flash was followed by the 'wrong' sound signal, that is, white noise after a light flash from the right and pure tone after a light flash from the left. In the misleading trials, the monkey still had to move the lever in the direction indicated by the sound signal, i.e., to the right after a tone and to the left after a noise, to gain reward.

Blocks of 100 discrimination trials and 30 blank trials (*see below*) were presented. In each such block only one ISI was used. The interval between successive trials was 2.5 s after a correct response, 5.0 s following an error, and 7.5 s if the monkey failed to respond. Successive blocks of behavioural trials were usually separated by blocks of passive stimulation in which the lever was inactivated and various acoustic stimuli were delivered to the idly sitting monkey.

Each behavioural block included blank trials. In such trials, the acoustic signal was not preceded by any light signal and lever responses were not rewarded.

In summary, each behavioural block included 130 trials. About 75 of them were normal trials in which the correspondence between the light and the sound signals was preserved. About 25 of the trials were misleading in that the association between the light and the sound signals was reversed. The remaining 30 trials were blank trials in which no light signals were employed. Presentation of the different types of trials was performed in a semirandom order (no more than 3 successive trials could be of the same type).

Surgical procedure

At the completion of behavioural training, the monkey underwent aseptic surgery in which a recording chamber was implanted over its left hemisphere. The monkey was anaesthetized and put in a stereotaxic apparatus. A point overlying the stereotaxic coordinates of the MGN was marked. A round skin flap was removed, and a round skull opening, 10 mm in diameter, centred on the marked point, was made. A Plexiglas recording chamber was centred on the marked point and cemented to the skull. The same procedure was used at a later stage in the experiment to implant a second recording chamber over the contralateral auditory cortex.

Recordings

In each recording session the monkey sat in the primate chair with its head restrained by a specially designed collar. Head position was fixed with respect to the speaker, the lights, and the spout from which reinforcement was given. The speaker was placed 60 cm directly in front of the monkey. Its frequency response was calibrated in this position, and a 12 band equalizer was used to improve its linearity within a range of 100 Hz to 22 kHz.

The recording chamber was fitted with a ball-joint manipulator (Hocherman *et al.*, 1981b) that was aimed at a specified stereotaxic point. A platinum-iridium microelectrode with impedance of 0.5–2.0 M Ω at 1000 Hz was advanced into the brain in 0.5 mm steps. An average auditory-evoked potential (AAEP) was recorded at each step. The recording mode was changed into extracellular recordings of single unit activity at a depth where a large amplitude, nonhabituating AAEP occurred.

The response of each unit to tones of different frequencies was first investigated as follows. The lower and upper ends of a frequency range were selected. This range was automatically divided into 100 frequency steps, which were then applied in a random or sequential order, at a fixed intensity of 60 dB SPL. The range of frequencies was changed several times and various stimulation rates, from 4/s to 1/2s were applied, until a tone frequency which evoked the strongest response was identified. This procedure was occasionally repeated with lower stimulation intensities to help select an optimal tone stimulus. The selected tone was then presented in blocks of 50 stimulation trials, in which the ISI changed randomly between 1.0 and 1.7 s (passive stimulation). The response to white noise stimuli, at 60 dB SPL, was recorded using a similar procedure. Recordings of unit activity continued with behavioural blocks of stimuli, separated by blocks of passive stimulation. When recordings from a given unit were completed, the electrode was advanced at least 100 μ m in depth before isolation of another unit was attempted. Each recording session terminated when the monkey was satiated, which usually happened after 6 h. The electrode and the manipulator were removed and the monkey was taken back to its home cage. After completion of the recordings from the left MGN, a second recording chamber was implanted over the right hemisphere. This chamber was used to record the activity of ACx neurons.

Data analysis

During the recording sessions the monkey's reaction times, percentage of correct responses, and unit activity were displayed on-line on a CRT and stored in digital form on a magnetic disc. Peristimulus time histograms (PSTHs) were plotted off-line for each type of trial. There were 6 types: normal trials with tone, normal trials with noise, misleading trials with tone, misleading trials with noise, blank trials with tone and blank trials with noise. All unit responses were quantified, and response differences between normal and misleading trials with the same acoustic signal were tested statistically, based on the normal approximation to a Poisson distribution (Z test), which was assumed to represent the neuronal rate of firing.

The response intensity of each neuron to tone and to noise signals in blank trials was used as a baseline measure of its responsiveness during task performance. The response to each of these signals, in every type of discrimination condition, was expressed as a percentage of the baseline response to that stimulus. This measure of responsiveness was defined as relative response intensity (RRI). The responsiveness of each neuron during task performance was thus characterized by 4 RRI values. One such value reflected the neuron's responsiveness to tone in normal trials. The second reflected the neuron's responsiveness to tone in misleading trials. The third and fourth RRI values reflected the neuron's responsiveness to noise in normal and in misleading trials, respectively.

RESULTS

Behavioural performance

The monkey's performance of the task was assessed by the use of 2 variables: percentage of correct responses (score) and reaction time. During training, when misleading trials were first introduced, the score in normal trials averaged 90% while in misleading trials it averaged only 10% (fig. 1A). This difference persisted for 5

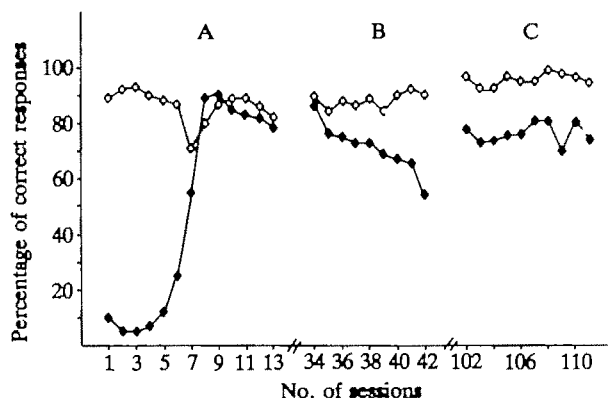


FIG. 1. Performance of the monkey in the discrimination task during training (A, B), and during the recording sessions (C). The average percentage of correct responses (ordinate) in normal trials (NC, open diamonds), and in misleading trials (MC, closed diamonds), in each session, is shown as a function of session number (abscissa). A, 13 consecutive training sessions, starting from first introduction of misleading trials. B, 9 consecutive training sessions, starting from first introduction of blank trials. C, 10 consecutive recording sessions.

sessions, in which the monkey's behaviour was obviously controlled by the lights. Within 2 more sessions behaviour came under control of the sounds, as indicated by the equally high scores in normal and in misleading trials. Another change occurred when the response period was shortened to 0.5 s and blank trials were added to the paradigm (fig. 1B). The score in misleading trials declined without a parallel reduction of score in normal trials. Overtraining caused this behaviour to stabilize. During the recording experiments a high score in normal trials and an intermediate score in misleading trials was maintained (fig. 1C).

Results of the reaction time analysis across all the recording sessions are shown in fig. 2. It can be seen that a correct lever push in misleading trials had on the average much longer latency than in normal trials ($P < 0.0001$). This finding corroborates the assertion that in such trials the monkey anticipated the wrong acoustic stimulus.

MGN neuronal activity

General description. The activity of 65 MGN neurons was studied in detail. All these neurons responded to noise signals and 62 neurons to tone signals. The most common response pattern consisted of an 'on excitation' followed by a sustained increase in firing (40 neurons to noise and 29 to tones). Pure on responses were evoked in 7 neurons

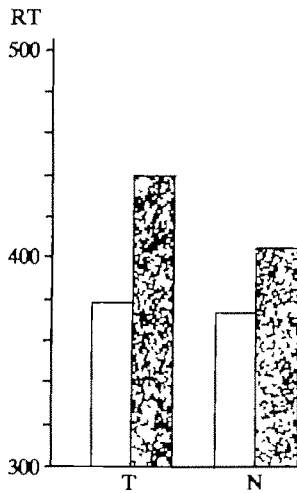


FIG. 2. Average reaction time (RT) values of correct responses, in ms (ordinate), following tone (T) and noise (N) signals, in normal trials (open bars), and in misleading trials (closed bars). SEM values are not indicated because of their very small sizes.

by noise and in 12 by tones. In 13 neurons sustained responses to noise, not preceded by a distinct on component, were discerned. Similar responses to tone stimuli were obtained from 10 neurons. Off responses and inhibitory responses were found in 5 neurons for noise and in 11 for tones. The response of all neurons was robust and followed stimulation rates of up to 2/s without signs of habituation. Optimal stimulation frequencies ranged from 0.5 to 22 kHz, depending on the position of the recording electrode. A systematic change from low to high optimal frequencies corresponded with a caudolateral to rostromedial shift in electrode position. However, no rigorous study of tonotopic organization was conducted and no attempt was made to determine the full shape of each neuron's tuning curve. Still, at 60 dB SPL most neurons responded to tone frequencies within a range smaller than one octave.

Response in discrimination trials. A comparison of evoked neuronal activity in normal and misleading trials revealed a significant response intensity difference (Z test, $P < 0.05$) in 21 neurons (32.5%). Fig. 3 illustrates a case in which the tone-evoked response in normal trials (lower right PSTH) is more intense than in misleading trials (centre PSTH). The top PSTH plots the difference between the lower 2 histograms.

Similar analysis of this neuron's response to noise shows momentary differences between the two discrimination conditions, but no overall difference in response intensity (3 left PSTHs). Fig. 4 shows a case in which the response to noise in normal trials (bottom right PSTH) is considerably smaller than in misleading trials (top right PSTH), while the tone-evoked response in normal trials (bottom left PSTH) is about the same as in misleading trials (middle left PSTH).

Figs 3 and 4 demonstrate two important points. (1) Greater responsiveness could be found either in normal trials or in misleading trials. (2) Most of the affected neurons (18/21) showed a significant response intensity difference for only one of the two sound signals.

The total MGN neuronal sample was divided into 3 categories. One included all neurons

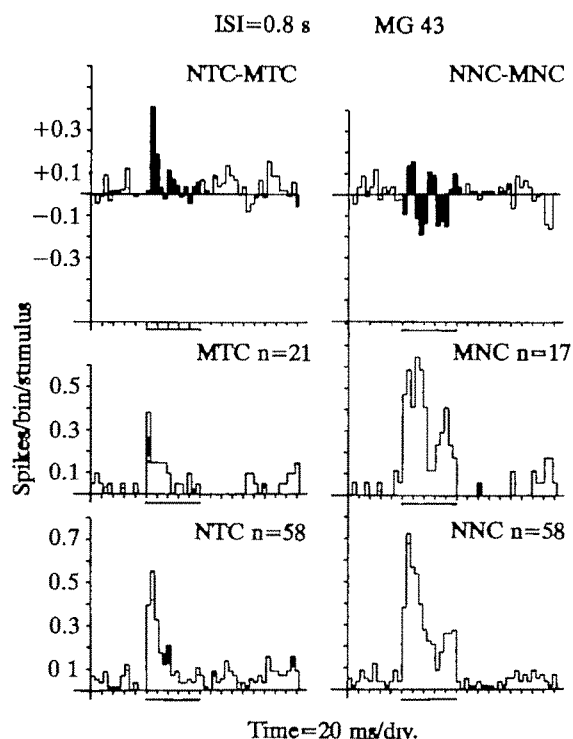


FIG. 3. Response of an MGN neuron (neuron MG43) to a 19.5 kHz tone (*left PST histograms*), and to noise (*right PST histograms*), in discrimination trials. Each PSTH begins at a time 100 ms before onset of auditory stimulation, and covers a 400 ms time period. Time of acoustic stimulation is marked under each histogram by a horizontal bar. Activity is given in terms of spikes/bin/stimulus (y axis). The number of trials averaged in each histogram is given at its top right corner. The neuron's response to the tone in normal trials with correct lever pushes (NTC) is shown by the bottom left PSTH. The neuron's response to the same tone in misleading trials with correct lever pushes (MTC) is shown by the middle left PSTH. The top left PSTH shows the activity difference between the NTC and MTC conditions. Similarly, that neuron's response to noise in normal trials (NNC) and in misleading trials (MNC) is shown in the bottom right and middle PSTHs, respectively. The response difference between these 2 conditions (NNC-MNC) is shown by the top right PSTH. In the difference histograms, the bins which correspond with the time of acoustic stimulation are blackened. ISI = 0.8 s.

whose response in normal trials exceeded that seen in misleading trials. The second included all neurons that did not show a significant response difference between normal and misleading trials. A third group included all neurons which responded more vigorously in misleading trials.

The number of neurons in each of these categories is listed in the Table. The number of neurons which responded more vigorously in misleading trials was twice that of the neurons which responded more vigorously in normal trials. However, this difference was not statistically significant (χ^2 test, $P < 0.1$).

Analysis of relative response intensity

The responsiveness of each neuron to the 2 acoustic signals was characterized by 4 RRI values, as described in the Methods section. Further analysis was undertaken based on the above grouping of neurons in 3 task related categories.

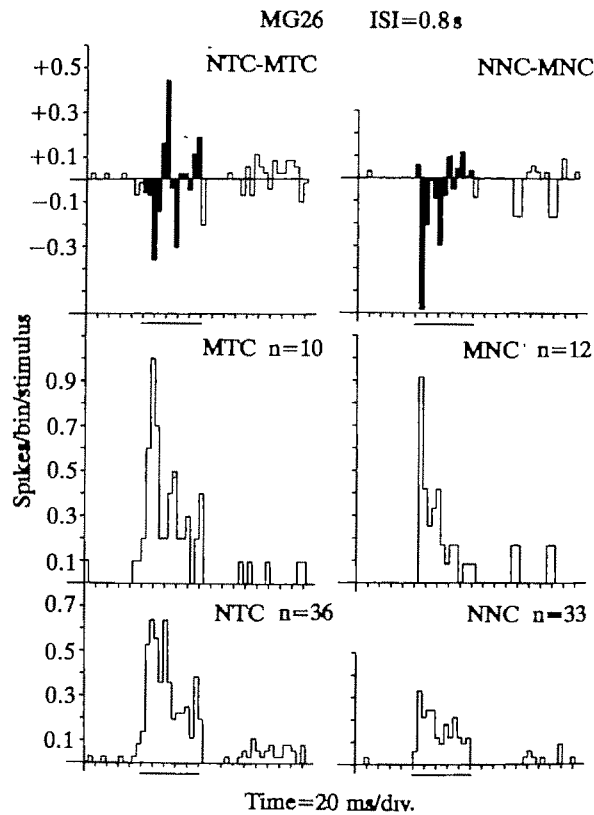


FIG. 4. The response of an MGN neuron (neuron MG26) to a 10.8 kHz tone (*left PST histograms*) and to noise (*right PST histograms*), in discrimination trials. All other details are as in fig. 3.

TABLE. DISTRIBUTION OF MGN NEURONS ACCORDING TO STIMULUS AND EFFECT OF ANTICIPATION

Stimulus	Total*	Class**	n	%
Noise	62	N > M	3	4.8
		N = M	51	82.3
		N < M	8	12.9
Tone	60	N > M	5	8.3
		N = M	47	78.3
		N < M	8	13.3

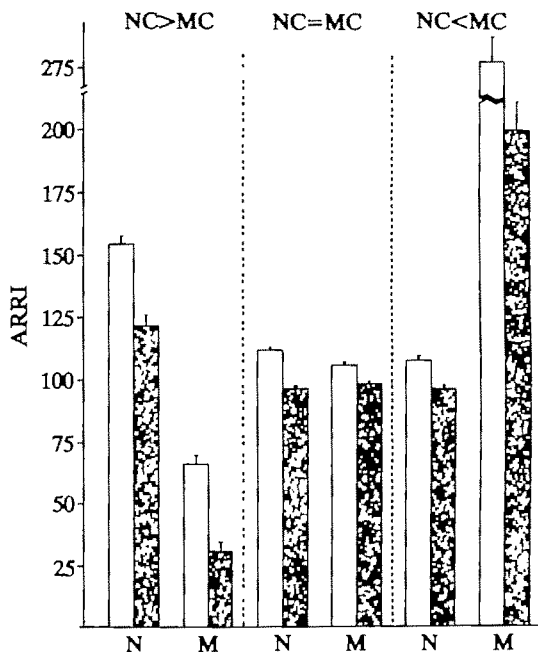
* Number of neurons whose response to the specified stimulus in normal (N) and in misleading (M) trials was compared. ** Classification of neurons according to whether the response in normal trials was greater than, equal to, or smaller than the response in misleading trials.

The RRI values of all neurons in each category were averaged in signal/condition groups. For example, the group of neurons whose response to the acoustic signal in normal trials was significantly more intense than in misleading trials provided 4 average

RRI values; for tone stimuli in normal trials, for tone stimuli in misleading trials, for noise stimuli in normal trials and for noise stimuli in misleading trials. The other 2 task related categories of units also provided 4 averaged RRI values each.

All averaged RRI values (ARRI) are plotted in fig. 5. For neurons that responded

FIG. 5. Average relative response intensity (ARRI) values of all MGN neurons. The total neuronal sample was divided into 3 main categories. One included all neurons whose response in normal trials was significantly greater than in misleading trials ($NC > MC$). The second included all neurons for which no response difference between the normal and misleading trials was found ($NC = MC$). The third category included all neurons whose response in normal trials was significantly smaller than in the misleading trials ($NC < MC$). In all cases only trials with correct lever push were considered. Every category was further subdivided according to whether the stimulus used was tone (open bars) or noise (closed bars). In each subgroup the relative response intensity was averaged for normal trials (N) and for misleading trials (M). The averaged relative response intensities (ARRIs) are expressed as a percentage of the neuron's response intensity in blank trials (ordinate). The vertical line on top of each bar represents one SEM.



to the acoustic signals in normal trials more vigorously than in misleading trials, the ARRIs were significantly greater than the 100% level in normal trials ($P < 0.0001$), and significantly smaller than the 100% level in misleading trials ($P < 0.0001$). The ARRI values for the group of neurons with no significant difference between normal and misleading trials were close to the 100% level for noise stimuli in both normal and misleading trials. For tones, however, the ARRI values were slightly higher than the reference level in both types of trials. The ARRI values for the group of neurons that responded more vigorously in misleading trials were close to the 100% level in normal trials, but were significantly greater than 100% ($P < 0.0001$) in misleading trials with both tone and noise stimuli.

It should be noted that the above tests compare neuronal firing in the reinforced trials with neuronal firing in the blank trials and are therefore independent of the criteria that were used to create the 3 neuronal categories.

Cortical neuronal activity

General characteristics. The activity of 107 neurons was recorded from the primary auditory cortex, contralateral to the MGN from which recordings were made. Cortical

neuronal activity was recorded under passive as well as during task performance conditions, following the same procedure used during MGN recordings. Most neurons (74%) responded to both tone and noise stimuli. Some neurons (14%) responded only to tones. The rest (12%) responded only to noise. In most neurons the response to both sound signals consisted of a brief on firing (99% of the responses to tones and 95% of the responses to noise). Only 4 neurons had an on-sustained response pattern.

Neuronal activity in normal and in misleading trials. The data obtained from 94 neurons sufficed for detailed analysis. A significant difference in response intensity between the 2 discrimination conditions ($P < 0.05$) was found in 25 neurons (27%). Of these, the response to tone differed in 14 neurons, and the response to noise differed in 13 neurons. The response to both stimuli was affected in only 2 neurons. More vigorous firing in normal trials was found with both tone (6 neurons) and noise (6 neurons). A greater response in misleading trials was again found with both stimuli (8 neurons with tones and 7 with noise). A typical example of a response difference to one stimulus but not to the other is shown in fig. 6.

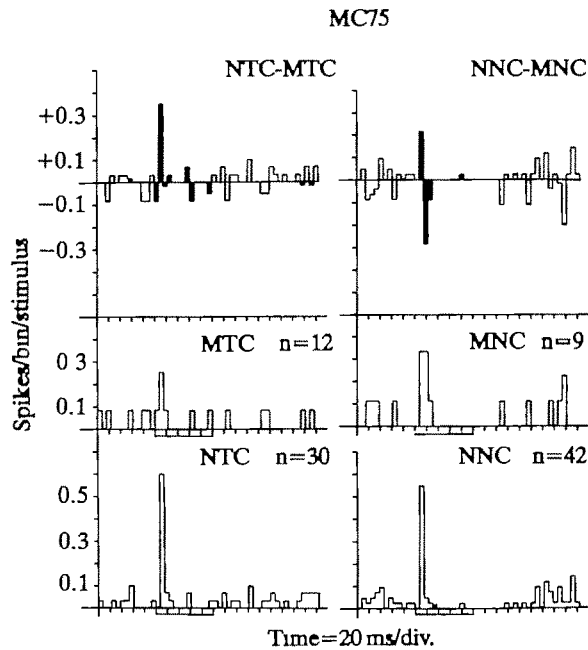


FIG. 6. The response of an auditory cortex neuron in discrimination trials. The response of neuron AC75 to a 4.8 kHz tone in normal (NTC) and in misleading (MTC) trials, and the response difference between these 2 conditions (NTC-MTC) is shown by the left 3 PST histograms. The response of the same neuron to noise in normal (NNC) and in misleading (MNC) trials, as well as the response difference between these 2 conditions (NNC-MNC), is shown by the right 3 PST histograms. Other details as in fig. 3.

Relative response intensity. As with the MGN sample, the cortical neurons were grouped into 3 categories (response in normal trials $>$, $=$, $<$, than response in misleading trials). The RRI values of all neurons in each category were averaged in the

appropriate signal/condition groups to produce ARRI values. The pattern of ARRI greater than the 100% level in normal trials and lesser than that level in misleading trials was found again for the group of neurons which fired more vigorously in normal trials (left part of fig. 7). In the 'indifferent' group all the ARRI were slightly but significantly above the 100% level in all stimulation conditions (fig. 7, middle). A pattern of ARRI at about 100% in normal trials and much above that level in misleading trials was seen in the group of neurons which fired more intensely in misleading trials, for the noise signal. With tones the ARRI in normal trials was slightly above the 100% level (right part of fig. 7).

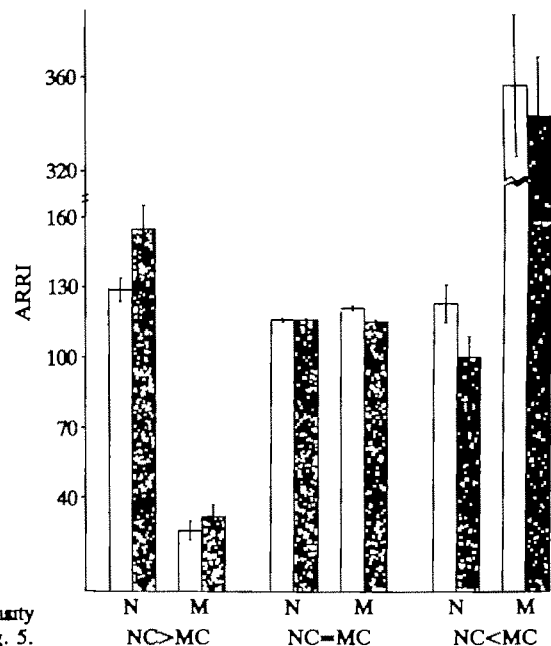


FIG. 7. Analysis of averaged relative response intensity (ARRI) of all cortical neurons. All other details as in fig. 5.

DISCUSSION

The present study shows that the response of some MGN neurons to acoustic signals depends on whether these signals are anticipated, thus indicating that transmission of information through the auditory thalamus can be controlled by behavioural contingencies.

The possibility of behaviourally related changes in the activity of auditory subcortical pathways was already considered by others. Gating of auditory information at the cochlear nuclei was suggested more than 30 yrs ago (Hernández-Peón *et al.*, 1956). Later, the brainstem auditory evoked potentials of human subjects were shown to be reduced by more than 37% in a selective attention task that required concentration on visual signals and neglect of auditory stimuli (Lukas, 1981; *but see* Wiederhold, 1986). A specific increase in the metabolic response of all auditory brainstem nuclei to an aversively conditioned tone signal was demonstrated in rats (Gonzalez-Lima and Scheich, 1984).

Finally, an alteration of cochlear micromechanics was recently demonstrated in human subjects performing a selective attention task. This change was attributed to active CNS modification of the cochlear transduction process prior to sound replication (Puel *et al.*, 1988).

Attempts to delineate behaviourally dependent changes in subcortical neuronal activity have involved mainly the IC and the MGN. A response increase in about 57% of monkeys IC neuronal sample was found to correlate with performance of a reaction time task (Ryan and Miller, 1977). Other researchers, however, were unable to see modulation of IC neuronal responses in relation to appetitive conditioning, but showed such modulation in neurons of the magnocellular (Mc) portion of the MGN (Birt and Olds, 1981). Some studies showed that appetitive (Birt and Olds, 1981) and aversive (Ryugo and Weinberger, 1976) conditioning do not modulate the activity of neurons at the parvocellular (Pc) part of the MGN. However, responses of the monkey's MGN-Pc neurons were found to modulate during performance of an auditory discrimination task (Gilat and Perlman, 1984). In summary, it is possible to conclude that the response of some subcortical auditory system neurons depends on behavioural contingencies. Whether this is also true for the MGN-Pc remains controversial, possibly because of the differences in behavioural techniques that were employed in various studies. This notion is corroborated by the finding that different modes of attention produce opposite changes in the human N1 auditory evoked potential (Parasuraman, 1978).

Effects of anticipation on MGN and cortical neurons

Finding that a thalamic neuron responds more vigorously to an anticipated (or to an unanticipated) acoustic signal is of limited interpretability. The absolute changes in neuronal membrane excitability, consequent upon anticipation of a particular signal can tell more about the involved mechanisms. However, with extracellular recordings we were unable to accomplish this goal directly. Instead, it was possible to define a reference state of activation for each recorded neuron and use it to assess anticipation related differences in response intensity. It should be stressed that the measure of relative response intensity (RRI) was independent of the response differences found between the normal and misleading experimental conditions. Thus it was possible to examine the RRI characteristics of the neuronal groups which were formed by contrasting the firing in normal and misleading trials. This analysis revealed that the responses of neurons which fired more vigorously for anticipated acoustic signals were actually suppressed when another signal was anticipated. In the past (Hocherman *et al.*, 1981a) we proposed that such neurons be regarded as 'signal matchers', being propositionally involved in a comparison between actual and anticipated signals. Other interpretations are of course possible; for example, such neurons may participate in transmission of the signal along a pathway which by its selection identifies the content of the signal and thus enables immediate action. A similar analysis for the group of neurons that responded more vigorously to unanticipated acoustic signals exposed a behaviour that we previously associated with error detection. In this case the response to anticipated signals did not diverge from background while the response to unanticipated sounds was highly facilitated.

Finding functions that suggest signal match and error detection in MGN neurons raises the suggestion that this level of the auditory system is actively involved in information

processing. Furthermore, recordings from the ACx and the MGN in the same animal revealed very similar effects of anticipation at both levels. The only difference between the MGN and ACx was an apparent increased responsiveness by the 'indifferent' cortical neurons, i.e., those neurons which responded with similar intensity in both normal and misleading trials. This difference may reflect either a differential effect of nonspecific attention at the two structures or a stimulus specific activation of the cortex (Posner *et al.*, 1988). Nevertheless, the similarity between the effects of anticipation at the MGN and ACx in the same animal (present study) and across animals is striking. Considering this, the fact that the MGN provides all auditory input to the cortex and the finding that the earliest cortical response components are modifiable, it is tempting to suggest that anticipation-related modulation of auditory information processing begins subcortically.

Anatomical localization

Evaluation of the present results depends on identification of the anatomical structures from which recordings were made. Unfortunately it was impossible to have detailed histological reconstructions of the MGN. Therefore, except for a good match between the stereotaxic localization of the MGN and the electrode positions which yielded strong acoustically driven recordings, and the size of the area from which such recordings could be obtained (2.0×2.5 mm), our identification of the thalamic recording site relies on physiological criteria. These begin with the recordings of averaged evoked potentials along the electrode penetration tracks. Small and quickly habituating AEPs were recorded along many electrode tracks in which only vaguely driven neurons were encountered. Only tracks that covered a small area in the centre of the recording chamber showed a dramatic increase in the AEP as the electrode tip reached the depth at which the MGN was expected. On these tracks, strong acoustic drive, lack of habituation and frequency selectivity were encountered. There can therefore be no doubt that the activity of MGN neurons was recorded in these experiments. Our main concern is that the part of MGN from which recordings were made needs to be conjectured. All physiological criteria indicate that our neuronal sample was gathered from the parvocellular part of the MGN. These criteria include lack of habituation, short response latency, narrow tuning, strong responses to simple acoustic stimuli, and response stability over time (Aitkin and Webster, 1971; Phillips and Irvine, 1979; Calford and Webster, 1981).

Interpretation

The present experiment can be viewed as a simple case of anticipation with minimal complexity of the relevant signals and of the choice situation. In real life anticipated signals and their choices can be much more complex. It is thus conceivable that the choice and implementation of anticipation requires the cortical machinery. Therefore the descending component of the auditory system, through which the cortex can control the excitability of the thalamic and other afferent stages, comes into focus. Indeed, an extensive corticothalamic projection system exists in parallel to the ascending thalamo-cortical system (Diamond *et al.*, 1969; Desmedt, 1975; Pontes *et al.*, 1975). The influence of the descending system on various MGN neurons was studied in anaesthetized cats by Ryugo and Weinberger (1976), who reported a differential effect on different types of MGN neurons.

A dual corticothalamic control network from the border of area 17–18 to principal cells of the lateral geniculate nucleus (LGN) and indirectly from the same area through LGN interneurons and the perigeniculate nucleus was demonstrated (Ahlsén *et al.*, 1982, 1985). This corticofugal system was inferred to control the gain for specific visual field features rather than to set the gain for LGN activation globally (Ahlsén *et al.*, 1985). A top down information flow was suggested by Haenny and Schiller (1988) for the visual system, using short-term memory and capable of 'selectively inhibiting or disinhibiting channels involved in processing of vision for accurate rapid and efficient discrimination behaviour'. It seems possible to apply the above theory to the present experiment, and to suggest that in the auditory system, the auditory cortex controls its own input by changing the excitability of MGN neurons. We suggest that this control is detailed enough to enable conditioning of specific signals, and that it is flexible enough to adapt to momentary circumstances. Further investigation is needed to clarify the physiological and anatomical details of this control mechanism and to determine its role in auditory information processing.

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A CENTURY OF CEREBRAL ACHROMATOPSIA

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SUMMARY

This review is an enquiry into why the early clinical evidence for a colour centre in the cerebral cortex of man was so successfully dismissed for the best part of a century. The imperfection of this evidence cannot be the reason, for the same evidence that was rejected earlier is accepted today. Instead, it was because the prevalent concepts of vision as a function, and of the role of the cerebral cortex in it, dominated facts and prevented acceptance of evidence showing a specialization for colour in the visual cortex. It was only after those concepts were overthrown by the demonstration of functional specialization in the visual cortex of the primate that the evidence for a colour centre in the human brain became acceptable. Today, our new knowledge of the colour areas and pathways in the primate brain allows us to give a more complete account of the pathophysiology of cerebral achromatopsia in man.

INTRODUCTION

For the best part of a century, the admittedly incomplete evidence for a localized colour centre in the visual cortex of man was dismissed, often with arguments that were both tenuous and crude. Rival theories, not equally well supported by facts, held sway. Dismissal of the evidence for a colour centre, with all that it implied for understanding the organization of the visual cortex, was to retard immeasurably the development of current views on the visual system and on brain function. It is naturally tempting to look for a cause in one or more illustrious individuals who were hostile to the notion. Such names are not difficult to find. Henschen, von Monakow, Holmes, Lenz, Lashley and Teuber, among others, were all hostile to the idea and yet none marshalled evidence that might be considered acceptable even by the standards of earlier times and the evidence of some, for example Lenz (1921), spoke clearly in favour of a colour centre. That they nevertheless managed successfully to discount the notion implies that the intellectual climate was more sympathetic to their views, for reasons that this article tries to uncover.

In approaching the problem, it became increasingly obvious that it was not the evidence itself, incomplete though it was, that dictated whether the idea of a separate centre for colour was acceptable or not. The very evidence which was dismissed earlier has become acceptable today. It was not acceptable before because it was incompatible with the then current concepts of cortical organization and visual function. It is acceptable today because these concepts have changed and have been replaced by ones more hospitable to the notion of a cortical specialization for colour, as well as other attributes of vision. But neither the earlier concepts, nor the ones prevalent today, are derived purely from a study of colour vision. Indeed, colour vision seems to have played a very minor role in the evolution of earlier concepts though a more cardinal one in the genesis of the new ones.

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The aim, then, is to establish the conceptual framework that allowed the evidence for colour localization in the cerebral cortex to lie dormant, indeed to 'vanish' (Damasio, 1985), for over 80 yrs and only to be considered seriously after functional specialization in the visual cortex of the monkey, including a specialization for colour vision, was established. What new concepts did this experimental evidence introduce, and what old concepts did it displace, which made it possible for the clinical evidence to be finally accepted?

The first two parts of the review are heavily weighted in favour of the clinical literature for the simple reason that the evidence for a colour centre was erected, and dismissed, largely because of it. Much heavier weighting has been given to earlier clinical studies than to papers published after 1973. The latter are of course more accurate. But by that time the evidence for a colour specialization in the monkey visual cortex was already established (Zeki, 1973). The issue was no longer controversial for clinicians, though it was to remain so for another decade for the scientists. The third part includes more material from monkey studies because it was largely the evidence from these studies that was to modify our picture of the visual cortex and establish new concepts, in the context of which a cortical specialization for colour vision became acceptable. The final part attempts to interpret some of the features of cerebral achromatopsia described in the clinical literature in the light of new knowledge that has been acquired on the organization of the colour pathways in the cerebral cortex.

1. COLOUR LOCALIZATIONISTS AND ANTILOCALIZATIONISTS

The early evidence for a colour centre in the cerebral cortex

'Le centre du sens chromatique se trouverait dans la partie la plus inférieure du lobe occipital, probablement dans la partie postérieure des plus lingual et fusiforme' (Verrey, 1888).

Cerebral achromatopsia is a syndrome in which the patient loses the ability to see colours after cortical damage. This loss may be complete or partial and it may or may not be accompanied by other visual defects. The nature of the loss is markedly different from inherited colour vision defects due to retinal abnormalities. It is not the only colour vision defect which may be the consequence of cerebral damage. But it can be distinguished from colour agnosia, a condition in which colours are seen but not recognized, from colour anomia, in which colours cannot be named, and from the dyschromatopsias, which are colour confusion syndromes. The terms are not used consistently, however, some authors employing the term dyschromatopsia to include achromatopsia and others using it to describe incomplete achromatopsias. In this paper, the term dyschromatopsia is used for colour confusion alone, the term achromatopsia being used for colour blindness. There are many descriptions of achromatopsia in the clinical literature. But the description by Verrey (1888) of a complete *hemiachromatopsia* might have been a turning point in the study of colour vision and of brain function, if only his evidence had been accepted. But it was questioned in the very year of its publication.

Verrey's description was not the first. One of the earliest, and more remarkable, cases of achromatopsia is that of Steffan (1881). His patient was a colour printer who had, therefore, a keen eye for colours before suffering a stroke at the age of 61 yrs which

left him with a total bilateral achromatopsia without an accompanying scotoma or a reduction in visual acuity. Examination of the patient 4 yrs after the onset showed that the achromatopsia, though still present, had become milder. In particular, he was able to perceive certain colours (red, yellow and blue) but only if they were made very intense, a phenomenon since noted by others. He had nevertheless a severe disturbance, particularly in his perception of red and green. Although he had no postmortem verification, Steffan nevertheless thought his case to be '... so ideally pure that henceforth no one can very well entertain any doubt concerning the existence of pathological colour blindness without any kind of amblyopia, hence that there is a special centre for colour vision in our central organ'. Soon thereafter, Brill (1882) described a patient who, following a cerebrovascular lesion had suffered from colour confusion, limited to certain colours, but without a hemianopic defect or loss of acuity. Brill had also studied the brain postmortem and found that the damage involved the cuneus, the calcarine fissure and part of the lingual gyrus (fig. 1A). This was extensive by later

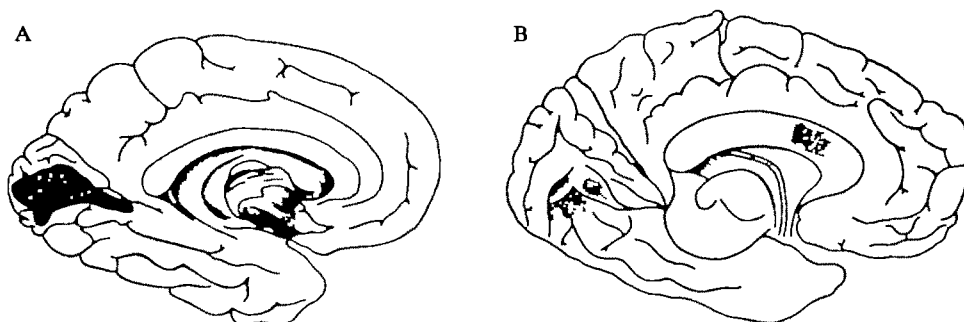


FIG 1 A, fig. from Brill's (1882) paper, showing the extent of damage in his patient, B, fig. from the paper of Verrey (1888) showing the extent of damage in his achromatopic patient.

standards, but more limited than previous descriptions. After reviewing earlier cases of colour blindness, Brill wrote '... so that my case seems to be the only one in which the existence of color blindness being positively established, a limited lesion justifying a physiological inference was found'. He supposed that there are two visual 'fields' in the cerebral cortex, side by side, 'of which limited lesion in one will produce hemianopia and extensive lesion of the other, a slight general diminution of color ...' (Brill, 1882). He supposed further that the colour 'field' occupied the calcarine fissure and its neighbourhood. Swanzy (1883) was more emphatic. Following an analysis of the first few reported cases of achromatopsia, of which he thought that 'mine is probably the most interesting', he wrote that '... they go to prove that the centre for colour perception is situated in the brain, and not in the eye or peripheral parts of the optic nerve, and moreover that in the brain it is a separate centre, distinct from that for the form sense and for ordinary light perception'. Soon after Wilbrand (1884), again relying on early cases of achromatopsia, developed an ingenious and surprisingly far-sighted view of the organization of the visual cortex. Like Swanzy, he supposed that there were separate cerebral centres for colour, for form and for the 'light sense'. He believed

that all optic nerve fibres enter the light sense centre first, where only the fibres concerned with the light sense end. The fibres concerned with the form and the colour sense pass on to the next (form) centre, where only the form fibres end, leaving the colour fibres to terminate in the last (colour) centre. He thought that these three separate visual centres were all part of the primary visual receptive area but that they resided in different layers within it. To account for cases of cerebral achromatopsia, he supposed further that these different layers could be individually injured. Gowers (1888) stated that '... the symptom [hemiachromatopsia] probably depends on disease of one part of the occipital lobe, and is proof of a separate centre for colour vision'. Unlike Wilbrand, however, Gowers imagined that the colour centre would be separate from that of 'light impressions', for he wrote that 'It is, on the whole, probable that all impressions go first to the region of the apex of the occipital lobe, since disease here causes absolute hemianopia, and that a special half-vision centre for colours lies in front of this' (Gowers, 1887). Yet proof of this and of the far-reaching theory of the separation of form, colour and light in the primary visual receptive centre was derived from studies on patients who were mostly either still living or on whom no postmortem examination had been performed. In brief, no information as to the extent of cerebral damage was available and the 'proof' could therefore be rightly questioned.

Verrey's study was different. First, unlike Brill's, his patient suffered from an absolute hemiachromatopsia, not merely a colour confusion. Next, through his postmortem examination he was able to state with an accuracy that is remarkable, even for the days of computerized tomography, that the colour centre is located in the lingual and fusiform gyri (fig. 1B). The relationship of these two gyri to the calcarine, or striate, cortex was unfortunate for a theory of a separate colour centre in the cerebral cortex. The lower border of the striate cortex, in which the upper field of the view is represented, extends onto the lingual gyrus, next to which lies the fusiform gyrus. The likelihood of the calcarine cortex being involved in any lesion, with a consequent scotoma, was therefore high (*see* fig. 2). The presence of a scotoma made it naturally easy to suppose that the defect in colour vision was due to involvement of the calcarine cortex itself, a view strongly championed by Henschen and others.

Like Eperon (1884) and Gowers (1887), but this time based on autopsied material, Verrey supposed that the three cortical centres did not occupy separate layers, as Wilbrand had imagined, but separate regions of the primary visual receptive centre in the occipital lobe because his case '... speaks in favour of a spread disposition of the three centres and not for their stratified disposition. Except that these centres ... are spread from above downwards, from the region of the first occipital convolution at the base of the occipital lobe, to the lingual and fusiform gyri'. Verrey thought that the most dorsal of the three centres was the 'light centre' and the most ventral the colour centre, with the form centre occupying the middle because in his case, as well as in that of Eperon, the form centre was the one 'which ... after the centre for the chromatic sense, had suffered most' (Verrey, 1888); in other words that the achromatopsia was accompanied by some difficulty in form perception. It will be evident from this that, at that time, neurologists thought that there were three qualitatively different kinds of vision. 'Light impressions' were studied by using white or black paper, 'colour vision' was studied by using coloured papers, and 'form vision' was usually studied relatively crudely, for example by noting whether the patient could read or count fingers.

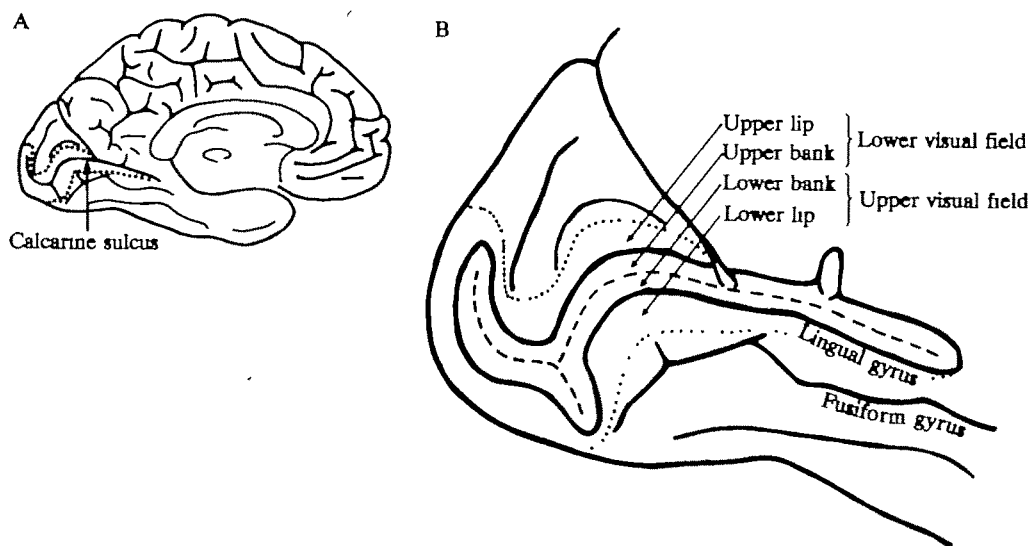


FIG. 2 A, medial view of the brain to show the relationship of the calcarine sulcus to the lingual and fusiform gyri, B, enlargement of part of A to show the representation of the upper and lower retinal quadrants in the banks of the calcarine sulcus.

The publication of Verrey's paper did nothing to satisfy the sceptics. In the same year, an article by MacKay (1888) urged caution and '... the desirability of investigating cases of hemianopsia of all kinds with more thoroughness and precision than is usually shown ...', adding with particular reference to the achromatopsic syndrome, '(1) that the cases are very few in number; (2) that the clinical examinations have been generally incomplete; (3) that there has been no postmortem examination in any of them'. The satisfaction of one of these criteria, the postmortem verification of the extent of the lesion in Verrey's work, did nothing to modify MacKay's view. In a footnote, he wrote that Verrey's study '... arrives most opportunely to support my contention for more careful clinical study, and affords the additional interest of a postmortem examination'! (MacKay, 1888).

But 11 yrs later, MacKay brushed aside his earlier exhortations to others and changed his views on achromatopsia as a result of a single case of achromatopsia whose 'light sense' 'was not especially investigated for want of proper means at the patient's house'! The difference was that this was his own case (MacKay and Dunlop, 1899) which he believed '... to be the first complete case of the kind that has been submitted to postmortem examination', whereas Verrey's case 'was one-sided (only hemiachromatopsia) and showed a more extensive lesion of the cerebrum'. But even though 'one swallow does not make a summer ... the facts in this remarkable case, the first as far as we know, in which a *total* acquired colour blindness from a cerebral lesion has been supported by pathological examination, point strongly towards the conclusion that if there is a separate centre for colour, its seat is the grey matter of the fusiform convolution' since their lesion 'being still of smaller dimensions [than Verrey's] carries the prediction a stage further' (emphasis in the original).

The objections to the evidence

'Ein besonderes, von der Sehphäre getrennt liegendes Farbenzentrum etwa im hintern Abschnitt der Occipitalwindung (Lobus fusiformis), ist mit Nachdruck zu verwerfen' (von Monakow, 1905).

The evidence from his one patient may have altered the views of MacKay. It did nothing to alter the views of others who, over the coming years, were to voice the very criticisms levelled by MacKay in 1888, repeatedly. However, the type of objection had grown in number by the 1960s to include the presence of scotomas, problems of recovery from scotomas, the presence of defects associated with achromatopsia and cytoarchitectural problems. It is as well to examine these objections here, before reviewing the conceptual difficulties which made the evidence for a cerebral colour centre outside the calcarine or striate cortex difficult to accept.

Number of cases

When Verrey, and MacKay and Dunlop wrote their papers, the precise limits of the primary visual cortex, and the manner in which the retina is represented in it, were still subjects of dispute. The latter especially required the examination of a very large number of haphazardly placed lesions, occurring through natural causes or as a result of gunshot wounds acquired in wars. Visual disturbances of a 'higher' order, such as the various agnosias and the achromatopsias, were commonly accompanied by scotomas, thus casting doubt on whether the defect was due to involvement of cortical tissue outside the primary visual receptive area and the optic radiations. For the achromatopsias, the scotoma was often peripheral while, by its nature, the colour blindness always involved central fields. This conjunction seemed an apparent contradiction. It created an awkward problem at a time when the topography in the striate cortex itself had not been fully worked out. We now know that in the prestriate visual area involved with colour vision in the macaque monkey, area V4, central vision is heavily emphasized at the expense of the periphery and that it has a topographic map vastly different from that found in the striate cortex (Zeki, 1977), with the consequence that a large lesion here should, theoretically at least, lead to defects in colour vision in central visual fields only. Clinical evidence suggests that this is also probably true for the homologue of V4 in the human. This evidence was not available at the time, when all explanations of perceptual defects in vision were made with reference to the primary visual receptive centre alone. Hence an emphasis on accumulating and describing an ever increasing number of patients before firm conclusions could be reached was common and violations of this rule were thought to be highly irritating. Thus Poppelreuter (1923), obviously greatly annoyed by the publicity which the case of mind-blindness described by Goldstein and Gelb (1918) had attracted, wrote 'In my book . . . I regarded it as more important to present in the first place the mass of new material in its purely factual aspects and to postpone the theoretical elaboration, which implies more or less a fixation of one's view, for a more leisurely postwar period. In this regard I find myself in outspoken opposition to Goldstein and Gelb who, in paradoxical contrast . . . have—on the basis of one single case—proposed a new theory of apperceptive mental blindness which I shall have to deal with in detail before I can present my own theory' because ' . . . the apparently copious utilization of an experimental psychological and phenomenological analysis, together with a skilful and vivid presentation, has lent the theory . . . the appearance of irrefutable correctness'

when in fact '... this case, which seemed sufficiently extravagant to have it filmed and shown to congresses' was built on a 'faulty interpretation of a peculiar defect'. And Henschen (1893) also relied on the number of cases in rebutting the evidence of von Monakow and others on the extent of the primary visual cortex (*see below*), noting that '... I have found in my hospital in Uppsala, nearly 40 hemianopic cases, supplemented in the postmortem records; whilst Seguin, in 1886, could only discover about the same number in the whole of literature'.

Naturally the addition of every new case of cerebral achromatopsia blunted this criticism somewhat, but did not silence it. Thus Campbell (1905) urged scientists to be 'cautious' in accepting the evidence and Lashley (1948) wrote 'Only the accumulation of numerous cases with adequate sampling of behavior in a wide variety of tasks can lead to a clear definition of the various types of defect resulting from brain injuries', no doubt because of the accessory problems encountered with almost every kind of visual disturbance resulting from involvement of cortex outside the striate cortex. Yet two facts emerge which make one wonder whether the dismissal of the evidence as late as 1948, and beyond, on the basis of the number of cases was justified. One is the central nature of the achromatopsic defect in every case, regardless of the extent of the scotoma, a fact rarely commented upon. The other is that in many reported cases of visual agnosias, such as 'mind blindness' (when a patient can see but cannot recognize objects), colour vision was not involved. In his review, von Stauffenberg (1914) listed several examples of patients suffering from mind blindness (*Seelenblindheit*) whose colour vision was not affected. At the very least, this should have suggested separate regions of the brain for form and colour vision. In sum, by the late 1940s a sufficiently large number of achromatopsic patients who shared certain common features had been accumulated to provide a *prima facie* case for suspecting a separate colour centre in the cerebral cortex.

The scotomas

From early times, the presence of a scotoma or a hemianopia became a cardinal point in dismissing the evidence purporting to show a separate localization for colour in the cerebral visual cortex. Whenever present, it implied an involvement of the calcarine cortex or the radiations leading to it. It is a fact that in the great majority of achromatopsic cases, there is an associated scotoma (for reviews, *see* Korner *et al.*, 1967; Meadows, 1974a). This was to be used as evidence for involvement of the primary visual receptive area in the cerebral cortex and against a separate centre for colours lying outside it, particularly by von Monakow and Henschen, who had opposing views on the extent of the primary visual cortex. The scotomas were variable in position, some being extensive, others more limited. When present, they involved without exception the upper visual fields, and hence the lower retinal representation, although some were more extensive. In the pre-1973 literature, the scotomas always involved the peripheral representation, but since then Damasio *et al.* (1980) have described 2 cases of achromatopsia in which the associated scotoma was limited to central fields.

There are nevertheless at least 2 cases in the pre-1973 literature of achromatopsias not accompanied by scotomas. Both are very rarely cited. The more interesting of the two is that of Steffan (1881). The other patient is described by Alexander (1881; but *see* Appendix 1). His patient had severe colour confusion, but no accompanying scotoma. Presumably, these cases are not usually cited because of the absence of postmortem

verification of the site of the lesion. Since 1973, at least 4 cases of achromatopsia without scotomas have been described (Mollon *et al.*, 1980; Young *et al.*, 1980; Kölmel, 1988; Sacks *et al.*, 1988). These cases are highly suggestive of a separate centre for colour in the cerebral cortex outside the calcarine area, one which can be compromised in isolation. But the fact that in most earlier cases, the lingual and fusiform gyri were only one of several cortical regions involved in a lesion gave greater weight to the scotoma-associated achromatopsias, making it easier for the evidence in favour of a separate colour centre to be disregarded.

The distribution of the scotomas could have given rise to some suspicion, but presumably there were not enough documented cases at the turn of the century, when the subject of a colour centre in the brain was being vigorously debated. There is no example of a cerebral achromatopsia accompanied by a scotoma limited to the lower quadrants only (Meadows, 1974*a*). The explanation for this is simple. The lingual and fusiform gyri are located ventrally and close to the lower bank of the calcarine sulcus where the lower retina, and hence the upper visual fields, is represented. Any vascular damage affecting the lingual and fusiform gyri is therefore more likely to damage the inferior bank of the calcarine sulcus. If it is extensive enough to invade the upper bank of the calcarine sulcus, and therefore the lower field representation, it is unlikely to spare the lower bank (fig. 2), hence the observation that the upper fields are always involved in cases of cerebral achromatopsia.

A more detailed examination of the scotomas associated with achromatopsia raises interesting points. The basic one is adequately formulated by Verrey, whose own subject showed a peripheral scotoma described as a 'mild, concentric retraction, from 15 to 20° in all directions' whereas 'in the integral half of the binocular visual field chromatic perception is abolished' (Verrey, 1888). The critical point here is that in the intact and still very extensive central visual fields, colour vision alone was compromised. As interesting are the scotomas in the patients of MacKay and Dunlop (1899) and Lenz (1921). In the former the absolute scotoma was ringlike and peripheral and included both the upper and lower visual fields. The achromatopsic field, however, was central and not accompanied by a scotoma, rather like Verrey's case. It is evident that the lesion must have been similar to Verrey's case, that is, situated in the region of the anterior lip of the calcarine sulcus and involving both its banks. This would explain the absolute peripheral scotoma. The lesions must have also included the lingual and fusiform gyri (in fact the postmortem examination revealed an involvement of the fusiform gyrus only) (MacKay and Dunlop, 1899). This would account for the central achromatopsia. The evidence from Lenz's patient was even more compelling. Here the absolute scotoma was limited to the periphery of the upper fields and was relatively small in size. The achromatopsia, however, was central and included the nonscotomatous field, that is, in a region where forms could be easily recognized. The lesion must therefore have included the lower lip of the calcarine sulcus, in addition to the lingual and fusiform gyri. This evidence was used by von Monakow (1905) to question Henschen's supposition that macular vision is represented anteriorly in the calcarine sulcus rather than posteriorly in the occipital lobe, but the associated central achromatopsia somehow made no impression on von Monakow, who denied to the end that a colour centre could be present in the lingual and fusiform gyri.

We may summarize the important facts as they relate to the scotomas in the following

way. (1) Cases of achromatopsia uncomplicated by a scotoma are very rare but they do exist. At least 2 are from the pre-1973 literature, yet neither was considered to be important. (2) There is no recorded case of an achromatopsia-associated scotoma which involves the lower quadrants only. The upper quadrants are involved in every case, a conjunction that can be accounted for by the anatomical disposition of the lingual and fusiform gyri in relation to the calcarine cortex (Meadows, 1974a). This association was not considered in the early literature. (3) There are at least 3 reported cases of extensive scotomas with macular sparing, in 2 of which colour vision was intact in the spared area (Peters, 1896; Bramwell *et al.*, 1915), while in the third colour vision was lost (Förster, 1890). The latter had an extensive lesion of the occipital cortex, involving the lingual and fusiform gyri. In Peters' case, the white matter alone was involved and a similar involvement is suspected, though not demonstrated, in the case of Bramwell *et al.* (see Symonds and Mackenzie, 1957). This should have strengthened the evidence implicating the lingual and fusiform gyri. Instead, Förster's case was used by both Henschen and von Monakow, each to support his own erroneous theory about the representation of the retinal macula in the cortex (see below).

In summary, whereas the presence of scotomas implicated an involvement of the striate cortex, constant features in their disposition, had they been seriously considered, would have raised important questions regarding the presence and disposition of a specialized colour centre outside the striate cortex.

The association of other defects with the achromatopsias

It is a fact that, in the majority of cases, achromatopsia is associated with other disorders. Prominent among these is prosopagnosia, or difficulties in recognizing faces (Meadows, 1974b). Indeed, there are many descriptions of achromatopsia in papers whose primary purpose is to describe prosopagnosia. Of these, one of the most famous is that of Dejerine (1892), where the achromatopsia is only briefly alluded to, in passing. All the achromatopsic patients summarized in the table of Korner *et al.* (1967) suffered from prosopagnosia and most had other defects as well, including alexia and a defect in orientation. Similarly, many of the patients with mind blindness summarized by von Stauffenberg (1914) had an associated achromatopsia. Such an association naturally led to some suspicion as to whether (1) the lesions were not larger than might have been supposed and (2) whether even smaller lesions might not produce more generalized defects, arguments which were especially appealing to Lashley (1948) and which led him to believe that the evidence concerning the specificity of defects following specific lesions was 'confusing and inconclusive'. There nevertheless remain cases in the pre-1973 literature in which the associated disorders were mild or nonexistent. Prominent among these are the cases of MacKay and Dunlop (1899), who did not suffer from a prosopagnosia but had an alexia, and that of Lenz (1921) who suffered from a transient topographical disorientation only. To this must be added the cases of Steffan and of Alexander, though in neither case was there a postmortem examination, making it awkward to reach definite conclusions. In addition, there are a number of cases of so-called hysterical achromatopsia in the early literature, some of which may have been of cortical origin, as Charcot supposed (de Schweinitz, 1906). In the more recent literature, the cases of Kölmel (1988) and of Sacks *et al.* (1988) are perhaps the 'cleanest', although the latter suffered from a mild transient alexia following his accident.

There is, however, an obverse of this picture which is rarely commented upon, namely that there are recorded cases of severe visual disturbances, including prosopagnosia, which either spare colour perception completely or affect it much more mildly. One such interesting case is that of Hécaen *et al.* (1957) who had a severe prosopagnosia and other visual disturbances of an agnosic nature, but with neither a field nor a colour defect. A similar case is described by Michel *et al.* (1986) where the prosopagnosia, following a unilateral occipitotemporal lesion which involved mainly the fusiform gyrus, was not accompanied by achromatopsia. Another case is that of Adler (1944) who suffered from a widespread visual disturbance, including a severe defect in form perception. Lashley (1948) alluded to this case in trying to dismiss the evidence for a specific visual disturbance following discrete cortical lesions. But Adler's patient had in fact to rely on colour for identifying objects and forms in her environment, suggesting a selective sparing of colour vision, a critical point to which Lashley makes no reference. A similar case is described by Wechsler (1933). Such cases, at the very least, supported the positive evidence suggesting a dissociation of colour. But this possibility seems not to have been considered although Wechsler himself drew the conclusion that 'colour perception and visual acuity can be dissociated in such a way that the former is preserved while the latter is impaired'.

In the fourth section of this review an attempt is made to explain these associated defects in the context of our present knowledge of the organization of the visual cortex. But, in the context of the knowledge available at the time, and until the 1970s, the association of other defects, both visual and nonvisual, with the achromatopsias constituted one of the most important arguments against the concept of the separation of functions in the cerebral visual cortex and was eagerly used by those hostile to the idea of a separate colour centre in the cerebral cortex. It is a pity that the relatively few cases of uncontaminated achromatopsia did not occupy a more prominent position in the dispute over this fundamental topic.

Postmortem examinations

This criticism may have been justified before the time of Verrey, but can hardly be said to have been reasonable after. The number of autopsied cases has continued to increase and, in every reported case of cerebral achromatopsia, involvement of the ventral part of the occipital lobe, and more specifically of the fusiform or lingual gyri, has been found. One of the most striking cases is that of Lenz (1921). Lenz's patient developed a (central) achromatopsia coupled to a relatively small and peripheral upper quadrantanopia, following a stroke (fig. 3). The autopsy revealed lesions in the optic radiation and the fusiform gyrus, with relatively little involvement of the striate cortex. But in reviewing his evidence against previous studies, Lenz considered that previous 'macroscopic' findings showed nothing more than that a lesion in any part of the visual pathway could lead to deficient colour perception while his own 'microscopic' studies of the pathology 'represent the beginning of systematic attempts to penetrate this great riddle of nature'. He concluded from his clinical observation and 'microscopic' examination of the brains that 'the clinical demonstration of a far-reaching dissociation between spatial and colour perception has led to the assumption of a special colour centre located in the fusiform gyrus, spatially separate from the elementary centre for black/white sensations. Wilbrand has previously pointed to physiological results [against this view]

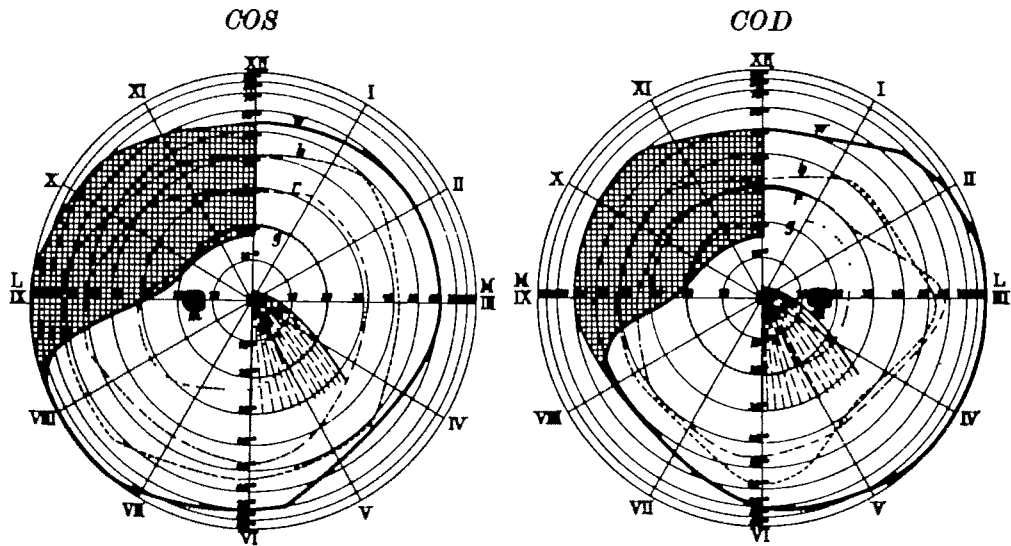


FIG. 3. The scotoma in the patient of Lenz (1921) The hatched area in the right hemifield represents the only region in which colour disturbance was not absolute.

and I have indicated the pathological anatomical findings which appear to render such an assumption untenable'. Here then was one of the best cases of achromatopsia ever described, with a small and peripheral scotoma, and supported by postmortem material which showed an involvement of the fusiform gyrus, the very cortical area already implicated. But it led to the conclusion that 'Einen Einblick in den Mechanismus der Farbenperzeption hat uns das Material nicht gebracht'! Lenz believed that the loss of colour perception arose from lesions in the white matter and the consequent interruption of impulse conduction, followed by some secondary atrophy and degeneration. This view was not greatly dissimilar to that adopted by von Monakow (1905) in trying to account for the visual agnosias and for achromatopsia. Thus even the postmortem examination, and confirmation that the fusiform gyrus was involved, obviously did little to satisfy the sceptics about a cerebral colour centre.

In summary, good postmortem material was available to link the achromatopsias to distinct lesions in the occipital lobes, but this did little to establish the case for a colour centre in the lingual and fusiform gyri.

Varieties of tests

Many of the tests used to study visual functions, including visual agnosias and achromatopsias, were relatively crude by the standards of today. The study of forms was especially elementary. The 'light' sense and the colour sense were, however, commonly studied perimetrically and essentially the same tests are used today. However, that even such elementary tests consistently revealed differences is interesting in itself, calling for further testing rather than the dismissal of the evidence.

In fact, an adequate test to explore all the subtleties of colour vision defects has yet

to be designed. One may test wavelength discrimination in the traditional way, or the ability to see constant colours, or coloured after images. The repertoire for testing visual functions in general is also increasing in relation to new knowledge that we are constantly acquiring. But there was nothing ambiguous about the tests employed in the past, or about the reports of the patients regarding their colour vision. Whether tests were carried out with Holmgren wools, or with patches of coloured paper, the subjects were asked to report the final result of all the processing in their visual systems, and that report was defective compared with normals. More significantly, all such achromatopsic patients had, and continue to have, one thing in common—they report the visual world, in all its variety of colours, as being composed of various shades of grey only. Since the normal visual world, unlike that of the laboratory or the clinic, is changing continually in both content and context, the patients are in a sense subjected to a variety of tests. The ubiquity of these reports, that the world always appears in shades of grey, suggests that a similar mechanism is malfunctioning in all such patients. Increasing the variety of tests would certainly have increased the amount of information. It would probably have done nothing to alter the basic observation, namely that their view of the natural world was devoid of colour.

An examination of these objections shows, then, that none constituted by itself serious or sufficient grounds for dismissing the evidence for a colour centre in the human cerebral cortex. To understand why the evidence was dismissed, it is necessary to look at the more powerful doctrines which were influential at that time and with which the concept of a colour centre was incompatible. To propose such an idea was to set oneself against firmly rooted concepts of the day.

2. THE CONCEPTS

Three concepts—the belief in the dual nature of the visual process and its representation in the cerebral cortex, the doctrine of a single, indivisible, ‘cortical retina’ to which all ‘visual impressions’ are carried, and the belief that functional differences are reflected in cytoarchitectonic differences—were to play cardinal roles in disregarding the evidence for a colour specialization in the cerebral cortex, outside the calcarine area. To propose such a specialization implied overturning these deeply held beliefs. Thus we find that, where the evidence was not disregarded, an attempt was made to account for it in terms of these concepts.

The dual nature of the visual process

Concepts of the representation of vision in the cerebral cortex were greatly influenced by the thinking of Munk and of Lissauer (1890). After studying a case of mental blindness, Lissauer had speculated about the cerebral processes underlying vision and concluded that they were essentially twofold. He wrote ‘. . . I subdivide this process into two acts which I shall try to separate from one another insofar as that seems possible. They are: 1, the act of conscious perception (cognition) of a sensory impression, which I designate as apperception; 2, the act of connecting other conceptions (ideas) with the content of the perceptions; this is an act of association.’ The term apperception derives from Leibniz and was popular among psychologists, especially Wundt, for a long time. Here I consider

it only as it influenced those concerned with the problem of visual representation in the cerebral cortex. Lissauer defined apperception further '... as the highest degree of perception, in which the consciousness accepts the sensory impression with maximal intensity'. He considered mental blindness to be a consequence of apperceptive disturbance. But he was less certain of the anatomical substratum of the postulated processes, writing that 'Mental blindness accompanied by partial defects of the still perceiving visual half would be of cortical origin; without these defects of transcortical origin'.

Such a view received powerful support from an unexpected source, namely the brilliant myelogenetic studies of Flechsig (1901). He had found that he could distinguish in the human cerebral cortex areas which were myelinated at birth. These he considered to be 'primordial', 'apperceptive' areas, receiving the afferent fibres from the sense organs. Next to them were areas which became myelinated later and which he called the 'intermediate' and 'terminal' zones. He had found that these different areas are constant in extent and position in all individuals of the same age. He saw in this arrangement a fundamental insight into cerebral organization, dismissing the views of Vogt and of von Monakow that the myelination may be related to fibre diameter or to the positions of the blood vessels as 'totally useless from a scientific point of view' (Flechsig, 1901). Different 'primordial' zones, of which the visual cortex was one, were separated from each other by the 'intermediate' and 'terminal' zones, which formed the association cortex (Assoziationszentren). The primordial areas did not communicate anatomically directly with each other. Instead they sent their fibres to the association cortex. The association cortex, on the other hand, was not connected directly with the sense organs, but received its input via the primordial zones. Flechsig therefore believed the association cortex to be the repository of 'psychic' functions (geistige Zentren, Cogitationszentren), areas which would play an important role in the associative stage of Lissauer. He obviously drew considerable satisfaction from the close correspondence between his 'primary' visual sphere, as myelogenetically defined, and the calcarine cortex, as defined by Henschen ('the most careful worker in the field' (Flechsig, 1901)), and which was beginning to be accepted as the primary visual area (fig. 4). He wrote 'As far as pathology is concerned I point to the work of Henschen on the circumference of the visual sphere in the occipital brain. We become more and more convinced that only the gyri on either side of the calcarine fissure . . . receive the visual radiation. No other part of the cortex

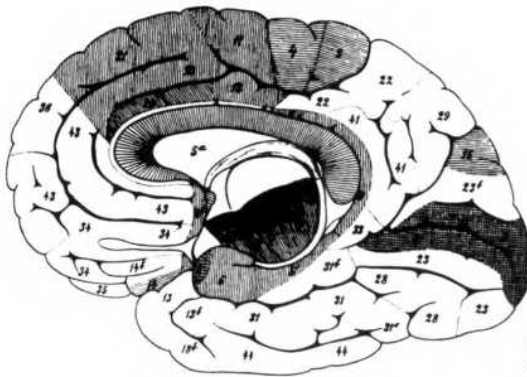


FIG. 4. Flechsig's diagram of the human brain to show the primordial areas (hatched and cross-hatched) and the association areas.

leads with certainty at least in man to a defect of the visual field and . . . the region . . . shows absolutely sharp boundaries . . . If only this field represents the entering place of the visual radiation into the organ of psyche we can delimit the functional circumference of the primary visual sphere in a very sharp manner' (Flechsig, 1905).

These ideas were soon to gain prominence among visual researchers, perhaps in a distorted and somewhat simpler form than originally intended by Lissauer and Flechsig. The *apperceptive* stage came to be thought of as one which involved the passive reception by a primary visual centre in the brain of the 'visual impressions', or image, formed on the retina. That image would include all visual attributes, that is to say form, colour, motion and so on. A defect in the apparatus, from the retina to the primary visual apperceptive centre, would result in the inability of the latter to receive all visual impressions, including colour impressions, and hence lead to a scotoma. A secondary, *associative*, stage would compare the received impressions and perceptions with previous impressions of a similar kind so that recognition and interpretation would become possible. In Henschen's simpler terms, 'one saw with the primary visual cortex and understood with the association cortex' (Henschen, 1930) (*see* Appendix 2). Thus Campbell wrote in 1905 of two areas ' . . . one specialised for the primary reception of visual sensations, the other constituted for the final elaboration and interpretation of these sensations' and Bolton (1900) wrote that 'A general review . . . shows that cortical visual representation has been described as twofold, consisting of a primary region in each hemisphere for the reception of impressions passing from the corresponding halves of both eyes, and a secondary, possibly psychic, centre in each hemisphere connected in each case with the opposite eye.'

The concept of a dual process, in which the first was devoted to the reception of all visual impressions in a single cortical area, made it difficult to accept evidence which suggested that one of the visual impressions, namely colour, would be received separately, in another cortical area, through a pathway that bypasses the striate cortex. To Henschen (1910) such a conclusion seemed absurd, ' . . . for with the calcarine cortex destroyed and the cortex of that other gyrus [lingual and fusiform] intact, the patient would then have to be absolutely blind and yet be able to see colours, which makes no sense'. We note here that no one was prepared to consider the possibility that there might be two or more stages in the visual pathways specialized for colour vision, one in the primary visual centre and another one outside it. That had to wait for studies of the prestriate cortex in the 1970s.

It is a striking fact that those set against the idea of a colour centre lying outside the striate cortex were convinced that colour is merely a 'visual impression' and must therefore be passively received by the primary visual cortex, which Holmes was later to qualify as 'a merely perceptive centre' (Holmes, 1945). They seem to have been little influenced by the writings of Helmholtz or of Hering or of Clerk Maxwell, all of whom had implied that colour was a much more intricate process and could not be classed as a mere visual impression and all of whom had been writing at least two decades before the crucial debates on the colour centres in the cerebral cortex. Helmholtz (1911) had written of colour vision as being ' . . . due to an act of judgement, not an act of sensation' and had tried to account for the most basic property of the colour system, colour constancy, by supposing that there is a mechanism of 'unconscious inference' which leads to 'discounting the illuminant' in assigning a colour to an object or surface.

Hering, his rival and bitter enemy, had also invoked higher factors in trying to account for the same basic phenomenon. He had written 'All the colours which we know, or those which we think we know, we see through the spectacles of our memory colours' (Hering, 1877). Clerk Maxwell (1872), in similar vein, had spoken of colour vision as 'a mental science', again implying the involvement of more active processes than the mere reception of visual impressions. Today, we may consider these attempts to account for colour constancy to be somewhat crude (*see* Land, 1974). But the statements quoted above acknowledged, implicitly at least, that 'higher' functions, such as learning, judgement and memory may be part of the process of assigning a correct colour to a surface and that to conceive of colour as an 'impression', passively received, may have been erroneous. Such views, had they been considered at all, might have led to the view that colour vision might involve cortical areas outside the primary visual cortex, indeed that, because of memory, it might involve 'association' cortex, as they conceived of it. From this it would have been but one step to the further notion that there may, after all, be more than one colour centre, one situated in the primary visual cortex and another situated outside it. But there is no reference in any of these clinical papers to the intricacies of colour vision (*see* Appendix 3). The entire debate about whether there is a specific colour centre in the cortex centred around the notion of whether there are two mutually exclusive primary visual areas, one for the reception of colour sensations and the other for the reception of other visual sensations.

By the turn of the century, under the weight of the evidence, the most far-reaching concession to a separate colour centre supposed that it resided in a separate layer of the striate cortex. Wilbrand (1884) had made this suggestion though Eperon (1884) and Verrey (1888) were both against the idea and it was soon forgotten. But it made a brief reappearance in 1923 in a remarkable conclusion reached by Poppelreuter from an examination of his patients. He wrote 'There has been no evidence for an exact point to point co-ordination between the retina and the calcarine cortex . . . There are several principles of topographic geometric projection (to the calcarine cortex), mainly these . . . We have a plurality of different systems, which are affected by defects in different ways and which can also remain functional in different ways, i.e., the defect shows itself as specific for different systems. The latter are . . . 1. Light-dark system; 2. Colour system; 3. Spatial (form) system; 4. Motion; 5. Orientation (or 'direction'). These systems show their specificity in that they can be disturbed relatively independently of one another, and in such a way that one can draw quite definite conclusions therefrom concerning the structure of the underlying physiological mechanisms.' Soon thereafter, Halpern and Hoff (1929), based on their clinical evidence, proposed that colour vision is localized to layers 2 and 3 of the striate cortex, a speculation derived from Pötzl, who based his speculations on the patients of Lenz. The proof here, like elsewhere in the history of achromatopsia, is too weak and the sometimes surprising arguments of Pötzl are derived at least in part from a consideration of Goethe's colour theory.

Many of the predictions made by Poppelreuter have been found to be true (*see below*) and today we would speak of parallel systems projecting to the striate cortex. But it is clear that none was willing to consider the possibility that both the primary visual centre *and* the visual 'association' cortex may be involved, and that they may both show submodality specializations, because of the underlying assumption that the primary 'impressions' are relayed to the primary visual cortex alone. Hence the notion that there

may be separate systems within the striate cortex, which connect with separate systems in the visual 'association' cortex, was never considered. It was not until the visual areas of the prestriate cortex began to be defined and their connections with the striate cortex studied, that this suggestion was made (Zeki, 1975).

The concept that vision is a dual process, and that the primary one was that of visual impressions, which included colour impressions, to be received by a primary visual receptive centre, prevented acceptance of the evidence for a colour centre lying outside this primary centre. To accept this would have been tantamount to accepting one of two equally unpalatable ideas: that colour may not be a 'primary' visual impression or, alternatively, that the primary visual cortex itself may not be limited to the calcarine cortex. Von Monakow and his school supported the latter view. In this, they were strongly opposed by Henschen. The victim was the notion of a colour centre outside the calcarine cortex, a problem that was almost peripheral to their arguments.

The definition of the visual cortex

'La rétine cérébrale est en même temps une rétine pour les impressions des couleurs' (Henschen, 1894).

A great deal of energy and debate was expended in the closing years of the last century and early parts of this in trying to define the extent of the primary visual cortex, with Henschen playing a leading role. He was among the first to describe the nature of the representation of the retina on the cerebral cortex. He supposed correctly on the basis of his anatomical and clinical studies that there is a cortical area which receives the fibres of the optic radiation and surmised, also correctly, that this area was coextensive with the striate, or calcarine, cortex. Like defects in visual perception in general, defects in colour vision, so Henschen believed, could only be produced by lesions of the primary visual (striate cortex) or the radiations leading to it and would invariably be accompanied by a more general scotoma or a hemianopia.

This notion of the striate cortex was not universally accepted, and was not to be so until well after the publication of the work of Campbell (1905) and of Brodmann (1905). Von Monakow especially had supposed that the retinal macula is represented throughout the occipital lobe (mobile retinal centre) and that the primary visual cortex was therefore much more extensive than the striate cortex, a formulation he based on the many examples of hemianopia which spared macular vision. In this he had the support of others, notably Lannegrace and Vialet. In 1889, Lannegrace had written, following his studies in the monkey, 'The optic fibres . . . irradiate over a considerable extent of the cortical convexity, from the occiput behind to the motor region in front; *the major part* of the fibres are concentrated in the occipital lobe . . . The visual zone, *zone of hemianopia*, is thus very wide; but it has its principal residence [*foyer*] in the occiput' (emphasis in the original). Thus for von Monakow and his followers the need to postulate a separate cortical visual centre outside the striate cortex and dealing with colour alone, was unnecessary. All the clinical evidence could be accounted for by the very large extent of the visual cortex, which went well beyond the confines of the striate cortex, or so they believed. The achromatopsias could also be accounted for by the widespread representation of the macula, where colour is emphasized, in the cerebral cortex. Moreover, the reported cases of colour vision defects were not of psychic disturbances

but sensory, apperceptive, ones, commonly associated with an incomplete disturbance in form vision as well. This idea was accepted half-heartedly by Vialet (1894) who disliked the ideas of Henschen which he described as 'une localisation à outrance'. Vialet wrote '... that the cortical centre for vision occupies the whole of the internal extent and that lesions of the cuneus, of the lingual and fusiform lobes and of the occipital point are capable separately to produce a hemianopia'.

Henschen was impatient with such a view, which he saw as a threat to his view of a single, indivisible, visual cortex with a fixed and rigid retinal map in it, the 'cortical retina'. Basing his argument on his clinical and pathological evidence, he wrote 'A hemianopia will thus result only if there is a lesion of this bundle [of Gratiolet] or the calcarine cortex' (Henschen, 1894). As for von Monakow's evidence, he wrote 'I will not enter into a criticism of these cases. The description of Vialet dispenses me' (Henschen, 1894). He considered Vialet's statement, given above, to speak against the concept of von Monakow's 'mobile visual centre'. Ewens' (1893) view that the angular gyrus (corresponding to the prelunate gyrus of the macaque monkey) might be involved in central vision (a perfectly plausible suggestion in the light of recent evidence) and that the striate cortex itself might be involved with peripheral and binocular vision (a less plausible suggestion), was dismissed as 'a theory in the air' (Henschen, 1894). Henschen proposed to call the 'visuosensory' cortex, coextensive with the striate cortex, the 'cortical retina'. He disliked the term 'visual sphere', preferring to use that term to describe visual cortex involved in 'psychic vision', that is to say a much larger cortical field than the 'cortical retina'.

In fact, there was nearly complete agreement between Henschen and von Monakow that there is no special colour centre in the brain, distinct from the visual receptive area. The only difference between them was their views on the extent of the visuosensory cortex. For von Monakow to acknowledge that there is a special centre for colour vision, outside of and distinct from the visuosensory cortex, was to acknowledge that the primary visual receptive area and the cortical representation of the macula was not as large as he had imagined. He therefore dismissed Henschen's views, and the evidence for a colour centre along with it, stating that 'Besides the one sided cortical colour blindness, there was almost without exception some loss of visual acuity, limitation of visual fields and at times also word blindness (Verrey, Henschen). In any case, no case of totally isolated cortical hemiachromatopsia supported by post-mortem examination has yet been reported' (von Monakow, 1905). For Henschen to acknowledge that defects in colour vision, to him also a primary visual 'impression', could obtain with lesions outside the 'cortical retina', as he had defined it, was to acknowledge that the 'cortical retina' was more extensive than the striate cortex. He therefore dismissed von Monakow's views and the evidence for a colour centre along with it, writing that 'As to the perception of colours, the commonly received opinion that it is situated on the ventral surface will not admit of criticism. Some of my own cases prove positively that colour perception is also situated in the calcarine cortex' (Henschen, 1893). As for the theory of von Monakow, it was '... based on an assertion without proof. Science does not recognize assertions' (Henschen, 1900). What of the evidence of Verrey and MacKay and Dunlop? They could also be dismissed. Henschen (1900) wrote 'The two cases of achromatopsia published by Verrier and Machay [*sic*] do not demonstrate, in my opinion, what these authors wanted to demonstrate'.

Disputes over the cortical representation of the macula

Here intervened another irritating factor for Henschen. He had supposed, mistakenly as it turned out, that central vision is represented anteriorly in the calcarine cortex and peripheral vision posteriorly. This supposition was strongly contested by von Monakow but for the wrong reasons (*see above*). For once, von Monakow (1905) used evidence which he otherwise cared nothing for, to attack Henschen's doctrine of the representation of the macula in the anterior part of the calcarine cortex, arguing that the case of MacKay and Dunlop (1899), with a peripheral scotoma following an anteriorly placed lesion, in the fusiform gyrus, was incompatible with Henschen's ideas.

He had at least seen the significance of one aspect of achromatopsia. Colour vision defects by their nature involve central vision and are often accompanied by peripheral scotomas, since the lingual and fusiform gyri are located anterior and lateral to the lower lip of the calcarine fissure, where the periphery of the upper visual fields in the striate cortex is represented. This circumstance probably accounts for the fact that Ewens, unsure of the exact boundaries of the visuosensory cortex, wanted to place central vision in the angular gyrus, i.e., anterior to the presently known macular representation in the striate cortex. This would at least account for the fact that achromatopsia, involving central vision, was usually the result of more anteriorly placed lesions. Henschen (1893) cared nothing for such evidence and wrote that the deductions of Ewens '... are too far removed from the solid anatomico-clinical facts to be the subject of a critical analysis'.

In fact, there were interesting cases of scotomas, involving colour vision, which cast doubts on Henschen's views concerning the representation of the macula. One of the earliest was that of Förster (1890). His patient had suffered a successive double hemianopia, but with a sparing of central vision. He suffered from spatial disorientation and loss of colour vision, but he could read and recognize small objects, though not large ones. At autopsy, Sachs found that there had been a large infarction, involving the medial aspects of both hemispheres, and including the fusiform and lingual gyri, but with the cortex at the posterior extremity of the occipital lobe apparently intact. Sachs concluded, correctly and in contradiction to Henschen's ideas, that the macula is represented posteriorly in the occipital lobes. Henschen (1900) dismissed the evidence, arguing for an involvement of the optic radiations and stating that '... this case proves NOTHING on the subject of the localization of the macula' (his emphasis). Von Monakow, on the other hand, saw in Förster's case support for his own theory of a widespread macular representation. He explained that little was known of the organization of the visual cortex 'in spite of the work of Henschen' but that 'it is only certain that this representation (of the macula) goes far beyond the visual area striata, for we know examples in which a man is deprived of both of his occipital lobes ... who not only has light perception from the smallest central field, but can even recognize objects ... and can even read (Förster's case)' (von Monakow, 1911). Yet we have on record another case published before these arguments were made, that of Peters (1896). Here there was also a complete, though unilateral, hemianopia with central sparing, as in Förster's case. But in this one, colour vision was preserved. Postmortem examination revealed degenerative foci in the white matter of both occipital lobes, without apparent cortical involvement—just the argument that Henschen had used to account for Förster's case, with central sparing and loss of colour vision. But neither Henschen, nor von Monakow, alluded to this case or to the insights it may have provided for understanding the colour

centres in the cerebral cortex, by asking why it is that colour vision was compromised in one but not in the other. Peters' case is not too easy to interpret today, but it may be conjectured that in his patient the lingual and fusiform gyri were intact, as were the pathways leading to them from the representation of the macula at the posterior extremity of the occipital lobe. Indeed, recent studies have shown a direct projection from the lateral geniculate nucleus to the prestriate cortex, including area V4 (Fries, 1981; Yukie and Iwai, 1981). More recently, Stoerig and Cowey (1989) have shown that 'blindsight' patients can discriminate wavelengths, presumably through this direct geniculoprestriate pathway. But in their anxiety to establish their views, the protagonists had little patience with such results and, if they were to consider them at all, did so merely to dismiss them. Thus the localization of colour was to be a casualty in a fight essentially concerned, not with colour at all, but with problems of localization, the extent of the primary visual cortex, the cortical representation of the retinal macula and whether it is 'fixed' or 'mobile'. Many years later, Henschen (1930) was to summarize it as follows: 'The famous brain scientist Const. v. Monakow . . . learned that, when a lesion affects some cells in the geniculate or in the visual centre, the visual impulse from the eye can be transferred in the geniculate or the visual centre to the adjacent cells. This theory completely dominated all his views on the operations of the brain. But if it is true that a sensory impulse can be transferred through an intermediary ganglion to several central organs, then there can be no distinct localization in the cerebral cortex. From this view he drew all the consequences and became so dominated by this new doctrine that, for the sake of the theory, he denied even the most undeniable facts. This was the case particularly as regards the visual pathway and centre, whereby he came into contradiction with his own experience. This (v. Monakow's) doctrine was disastrous for the development of the theory of visual function, and during almost thirty years he persistently fought the present author (Henschen) who, on the basis of facts, advocated a strict localization.' It is interesting to note here a study described by von Monakow in 1900. Reporting two cases of blindness, one acquired after neonatal infection, he remarks on the 'sparse anatomical findings in the occipital lobe despite permanent abolition of both optic nerves and considerable atrophy of the optic radiations'. This leads him to conclude that the occipital lobe must have compensated by taking over some other sensory function, thus supporting his views on the absence of a fixed localization in sensory cortex (von Monakow, 1900b).

In fact, with the extent of the primary visual cortex now well defined in primates, one is apt to forget that this was done relatively recently. Indeed, as late as 1939, the hostility that this definition had generated can be felt. Monbrun (1939) wrote 'This [Henschen's] concept of a "fixed projection" of the retina on the cerebral cortex . . . was fought for a long time . . . and above all by von Monakow' but 'War veterans with partial hemianopsia have not yet seen reappear the restitution of function so dear to Monakow' (in the context of his mobile centre theory).

The calcarine cortex becomes the sole visual perceptive cortex

'A l'heure actuelle, tous les auteurs sont ralliés à la théorie du centre [visuel] corticale unique' (Monbrun, 1939).

At any rate, with Henschen's doctrine of a 'cortical retina' established, the term visual cortex came to be equated with the calcarine cortex, and excluded all other areas, including

the 'visuopsychic cortex'. It also became common to try to account for all perceptual deficits in vision in reference to the calcarine cortex alone. Scotomas, due to lesions of the visual (i.e., the calcarine) cortex, soon acquired a disproportionate influence in interpreting the achromatopsias, and in dismissing them. The meticulously careful Holmes had studied the scotomas of patients with missile wounds acquired during the Great War, using white as well as coloured stimuli. He wrote 'My observations . . . tend to show that an isolated loss or dissociation of colour vision is not produced by cerebral lesions' (Holmes, 1918). In his Ferrier Lecture, he was more emphatic. He wrote ' . . . the striate area or visual cortex is merely a perceptive centre . . . The perception of colour also depends on [it]; mild lesions of the cortex which do not abolish perception of light frequently disturb colour vision; there is no evidence that this is subserved by any other region of the brain' (Holmes, 1945). In this, he was merely repeating what Marie and Chatelin (1915) had said years earlier, that 'It is, in effect, classical to consider hemiachromatopsia as resulting from a mild lesion of the visual sphere or the radiations'. Why mild lesions of the cortex should abolish colour vision specifically was not a question that he or Marie and Chatelin considered, as Wilbrand (1884) had. Damasio (1985) holds Holmes more responsible than I do for allowing the concept of central achromatopsia to vanish from clinical neurology, writing that 'His authority and the importance of his other superb observations cast a shadow on the descriptions of acquired achromatopsia', while I think that Holmes, like others, was a man of his times who subscribed fully to the then prevalent concepts, without enquiring further into their validity. On the other hand, Damasio is a good deal more generous than me towards Holmes and excuses his mistake on the grounds that his sample of World War I patients was 'highly skewed', most having dorsal parieto-occipital lesions and none exhibiting an achromatopsia. Yet Holmes' strong statements of 1919 and even stronger ones of 1945, quoted above, show that in the intervening 25 yrs he had not made any effort to enquire into why his patients never showed a central achromatopsia, in spite of the fact that this had been described in the literature. The fact that he does not cite any of this evidence excuses him even less.

More recently, Teuber *et al.* (1960) concluded from their perimetric studies that 'There is thus no evidence for a genuine dissociation . . . of color and form vision. The different tasks involved in perimetry tap visual performance at different levels of complexity. Seemingly selective impairment of one aspect of vision (e.g., color discrimination) reflects, we believe, a corresponding rank order in the vulnerability of different levels of function, in the presence of lesions in their common substrate', a conclusion almost identical to that of Magitot and Hartmann (1926) and Monbrun (1939). Here, implicitly at least, the striate cortex is no longer a merely 'perceptive centre' but is also involved in colour discrimination. That the question of cerebral achromatopsia resulting from lesions outside the striate cortex had become a dead issue can be ascertained by the fact that neither Holmes, nor Teuber *et al.* refer to any of the papers cited here. As with Holmes' interpretation, that of Teuber *et al.* is that colour vision resides within the striate cortex but is more vulnerable to cortical lesions. If so, then perhaps colour vision would be the last to be reinstituted in a recovery from scotoma. If that is the case, then perhaps it could be shown that achromatopsia is not due to a lesion in a separate cortical area at all, but merely the manifestation of a slower recovery of colour. It is a suggestion strongly implied, but not actually stated, by Monbrun (1939). But the recent

studies of Zihl (1981) show that recovery of visual functions in patients with scotomas, including a recovery in colour vision, can occur, provided the prestriate areas have not been compromised by the lesion and 'in the case of damage to the striate and the prestriate cortex, no return of colour vision . . . has been found'.

In summary, by the 1970s, the position was stated quite clearly by Duke-Elder (1970), that 'For all the theories, however, there is no substantial evidence and all the clinical and experimental data at our disposal point to the absence of a specific localization for the colour sense'. Even the possibility of colour agnosia, which Holmes (1945) had conceded could result from lesions 'in the neighbourhood of the visual cortex', came to be dismissed. Critchley (1965) wrote of ' . . . a mere handful of instances of alleged colour agnosia, most of which are unconvincing', adding that 'The wisdom and indeed the legitimacy of isolating from the medley of cases of disordered colour perception acquired as a result of brain disease, a particular entity to be known as 'colour agnosia' is doubtful. To do so would in the first place imply that over and above the perception of colours there exists in the normal state a localizable faculty of 'colour' gnosis. On the face of it this is improbable *and is out of harmony with current ideas of brain function*' (my emphasis).

Henschen and the colour centre in the striate cortex

But to dismiss the evidence in favour of a separate colour centre outside the striate cortex was obviously not enough. Henschen had to show that the defects in colour vision could be accounted for by supposing that a part of the striate cortex itself is specialized for colour vision. As we have seen, there was nothing new in this. Wilbrand (1884) had already suggested it and Poppelreuter (1923) had postulated an even more far-reaching separation of functions in the striate cortex, which included colour. Such a view was not, of course, to go unchallenged, even by those not particularly involved in the controversy of whether there is a cortical colour centre outside the striate cortex. Magitot and Hartmann (1926) thought that we should be 'prudent' in accepting such explanations because 'in admitting a chromatic functional specialization for the calcarine cells, should we admit equally the presence of specialized neurons in the optic pathways?' Really they had seen the point. Once the admission of specialization was made in one centre, the logical consequence was to postulate it for the regions feeding that centre. Many years later, the conclusion that the striate cortex must act as a functional segregator was drawn from the observation that it feeds the specialized areas of the prestriate visual cortex (Zeki, 1975).

Henschen's attempt to demonstrate this was anatomical in nature and came many years later, when the striate cortex was generally accepted as being coextensive with the primary visual cortex. It was published at his expense in 1930, in his eighty-third year, as the eighth and final part of his *Pathologie des Gehirns*. It is written in arcane German, sometimes grammatically incorrect and difficult to understand, no doubt explicable by the fact that he was ' . . . bedridden, which unfortunately has left traces in the editing of the text'. It has signs of hurt feelings, as when he says of the work of Alouf 'In his historical account on the striate cortex . . . he enumerates all investigators . . . with the exception of the one who was the first to give a detailed description of the area, namely Henschen . . . my name does not appear even in the bibliography' when in fact 'By comparison with my photos . . . I find Alouf's descriptions not only useless, but

incorrect throughout'. It is also obvious from reading this account that '... the seemingly intractable problem of the anatomical cerebral organization of colour perception ... which had been regarded as insoluble' was to haunt him to the end of his life and that he felt acutely the need to justify the fact that colour 'impressions' are received in the calcarine cortex, not elsewhere.

Henschen's starting point here is the lateral geniculate nucleus and his discovery of 'the principle of the size of cells' in the visual system. 'The principle says, the more peripheral the cells are situated in the visual centre, the larger are the cells; the central (macular) cells are almost invariably the smallest'. Striking was the fact that the upper four layers of the lateral geniculate nucleus, the parvocellular or P layers, have small cells whereas the lower two, magnocellular or M layers, have large cell bodies. 'But why are these (magnocellular) cells so large? I guess in order to be able to receive more light.' From this, he develops the view that the magnocellular layers deal with peripheral vision and therefore with the 'light' sense whereas the parvocellular layers deal with 'macular' vision and therefore with colour 'impressions'. This anatomical observation provides him with the material for a theory of colour, based on cell size. This theory supposes that throughout the visual system, large cells deal with the 'light' sense whereas the smaller ones deal with colour. He cites Max Schultze's discovery of the rods and cones in evidence. Translated to the cortex, he tries to account for colour specialization in the striate cortex by demonstrating that a particular kind of cell, the small cells of layer 4, are the colour cells and are to be distinguished from the much larger 'light' cells. Using cell size as a criterion, he states that 'as a centre of the colour sense it is always possible to designate the calcarine fissure ... There is not a single case in which the colour centre is not in the calcarine cortex'. But the precise position of the 'colour centre' he considered to be variable, and to include sometimes the whole of the calcarine cortex, to extend in others to the median surface of the cuneus and also to include a small section of the lingual gyrus. His 'evidence' rests largely on the fact that in the nocturnal loris, *Potto*, the whole of the calcarine cortex consists only of the large 'light' cells whereas 'in all other diurnal monkeys one finds two kinds of cell'. And since the small cells in the calcarine cortex of rhesus are less densely packed in the limbus than in the centre '... one can conclude without reservation that there is a higher intensity of colour perception in the centre than in the periphery where there is a lower density or even absence of colour cells'.

The spell of cytoarchitectonics

'Es genügt uns die Feststellung, dass sich architektonisch differente Gebiete fasersystematisch oder nach Zerstörung oder bei Reizung verschieden, bzw. gleich gebaute Rindstellen identisch verhalten' (C. and O. Vogt, 1919).

In the battleground on which the evidence for achromatopsia was dismissed, colour vision seems more like a tiresome irritation in a fight which was concerned more with the extent of the primary visual, or visuosensory, cortex. An important consideration in this was the cytoarchitectonic picture. Neurologists have traditionally believed that functional differences in the cerebral cortex are reflected in architectonic differences and, conversely, that an area of uniform architecture is also one of uniform function. This is undoubtedly so. But the method commonly used in the past, that of cytoarchitectonics, was not always equal to the task of revealing anatomical differences

between cortical areas. It was nevertheless to play a cardinal role, right up to this decade, in dismissing the evidence for colour specialization.

If there were a special colour centre in the cerebral cortex, outside the striate cortex, then it would have been reasonable to expect, so neurologists believed, that it would have a special architecture. Yet no one was able to delineate a distinct area in the fusiform and lingual gyri using the cytoarchitectonic method. The notion that some visual impressions would be received in a primary visual centre of one architectonic appearance while another, colour, would be received in one of another architectonic appearance ran counter to the view that a unique function, in this case that of receiving visual 'impressions', would be undertaken by an area of unique architecture although it is obvious that Monakow and his adherents, in supposing that the primary visual centre included both striate cortex and the area surrounding it, went against this doctrine. Attempts were therefore made, especially by Beck (1934), to subdivide the striate cortex cytoarchitectonically in an elaborate way. But others have found it very difficult to repeat his findings.

Brodmann's (1909) proposed subdivision of the cortex outside the striate area was into areas 18 and 19. These areas cut across the fusiform and lingual gyri, so that part of the cortex of each was characteristic of area 18 while the other of area 19. Bolton (1900) and Campbell (1905), using the identical wording, had considered that a cortex which is 'visuopsychic' in function was 'doubtfully existent and doubtfully located'. For Campbell, its existence was due to circumstantial evidence alone because '... the distinctive histological structure of this field of cortex ... strongly suggests that it possesses special physiological functions. Further, its close relationship to the visuosensory or calcarine area ... suggests in equal measure that it is the cortical field for visual psychic representation' (Campbell, 1905). But the ever-cautious Campbell nevertheless thought, with Delphic wisdom, that the visuopsychic cortex might contain 'one or more' areas, though he did not specify where one might look for them. Subsequent maps of the human brain, for example, those of von Economo and Koskinas (1925) and of Bailey and von Bonin (1951), have differed little from Brodmann's map. The difficulty of drawing a sharp boundary between areas 18 and 19 was acknowledged, and the problem dealt with by the expedient of using merging colours and renaming the areas OB and OA. Attempts have been made to subdivide Brodmann's areas 18 and 19 on myeloarchitectonic criteria. In particular, in a rarely cited work, Lungwitz (1937) proposed an elaborate subdivision, which included the delineation of the lingual gyrus and subdivisions within the fusiform. But the subdivision was not taken seriously by anyone, including Lungwitz himself, who doubted the validity of these divisions into subfields, although there is no allusion in his paper to the fact that clinical evidence had proposed a special function for the lingual and fusiform gyri. At the time that Lungwitz was writing, this evidence was dormant.

Even the modest subdivision proposed by Brodmann and half-heartedly supported by von Economo and Koskinas and by Bailey and von Bonin was disputed by Lashley. In an article strongly critical of cytoarchitectonic studies in general, Lashley and Clark (1946) wrote 'There is no present justification for architectonic subdivision of the occipital lobe anterior to area 17. Areas 18 and 19 are indistinguishable from each other and from area 7 and probably form a functional unit with part of the latter.'

This difficulty of subdividing the prestriate cortex, even modestly, was much to the

liking of Lashley who distrusted localizationist tendencies and the assumptions behind such subdivisions. While agreeing that different sensory modalities were associated with different cortical fields (Lashley, 1931), he nevertheless had propounded his theory of mass action which supposed that cortical areas contribute equally to the execution of complex tasks. Colour vision was, to him, just such a complex task. He thought that 'Dissociation of functions, as in isolated loss of colour vision . . . are less clearly referable to injury in any specific region' and quoted approvingly von Monakow's statement that 'I do not know of a single case in which a purely traumatic lesion in the occipital lobes of an otherwise sound brain resulted in a persistent visual agnosia' (Lashley, 1948). He thought that the clinical evidence for a 'secondary disorder' such as a defect in colour vision following specific cortical injuries was 'confusing and inconclusive' while 'The development of agnosia in toxic conditions . . . points to diffuse damage and disorganization rather than to focal lesions' (Lashley, 1948). To support his argument, Lashley referred to the work of Adler (1944) whose patient did indeed have a widespread agnosic disorder but whose colour vision was actually far less impaired, a sort of negative evidence in favour of a dissociation of colour which may be easier to interpret today, but which Lashley did not allude to (*see below*). Not taking this evidence into account, he believed that there was, therefore, little reason for ascribing 'such secondary disorders . . . to lesions in the cortex adjacent to the striate cortex' (Lashley, 1948), particularly since the latter cortex could not be subdivided into specific subregions on cytoarchitectonic criteria.

It was not to be the last time that evidence in favour of a specialization for colour was to be dismissed because of negative architectonic evidence. In a repeat of history, the physiological evidence for a colour specialization in the primary visual cortex of the macaque monkey was also dismissed by Hubel and Wiesel (1977), partly at least because of the architectonic uniformity within it. They had reported all cells outside layer 4C to be orientation selective, with one orientation succeeding another in an orderly sequence in a direction parallel to the cortical surface. This seemed at variance with other physiological evidence, which had shown that there are many wavelength selective cells in the striate cortex, of which substantial proportions are not orientation selective (Dow and Gouras, 1973; Dow, 1974; Poggio *et al.*, 1975; Bertulis *et al.*, 1977; Michael, 1978). It was also at variance with the theory of functional specialization in the visual cortex which predicted segregation of function within V1 (Zeki, 1975) supposing that, because the specialized visual areas of the prestriate cortex are fed their input from the striate cortex, the latter too must act as a segregator. The pursuit of the separation of the colour pathways within the striate cortex came only after the anatomical demonstration of its nonuniformity. More specifically, it came only after the demonstration that, when stained for the enzyme cytochrome oxidase, the striate cortex, far from appearing uniform, is characterized by a set of densely staining blobs, especially prominent in layers 2 and 3, and which are separated from each other by the more lightly staining interblobs (Horton, 1984; Livingstone and Hubel, 1984). Livingstone and Hubel (1984) have since shown that cells inside the blobs are predominantly wavelength but not orientation selective, whereas those outside are predominantly orientation but not wavelength selective. Such a functional segregation within the striate cortex, taken together with the isolation of motion detecting cells in layer 4B and upper layer 6 (Lund *et al.*, 1975; Shipp and Zeki, 1989a), is strongly reminiscent of the functional organization

of the striate cortex propounded by Wilbrand (1884) and more especially by Poppelreuter (1923). As to why this segregation was not reported in the earlier studies of Hubel and Wiesel, Livingstone and Hubel (1984) state that 'Without any anatomical hints of non-uniformity in the upper cortical layers, it would have been easy to dismiss occasional, apparently sporadic groups of non-oriented cells', although the distribution of blobs is not sporadic. It is nevertheless also a fact that it was colour vision which was to suffer most from such preconceived ideas resulting from cytoarchitectonic uniformity. Ocular dominance columns in the striate cortex were found by Hubel and Wiesel (1977) without any anatomical hints.

Thus we see that the cytoarchitectonic axiom was instrumental in shelving the evidence for colour specialization, not once but twice—first in the prestriate cortex and next in the striate cortex. Once again, the study of colour vision was to be a casualty because of other concepts, not themselves directly related to it.

3. THE REVISION OF CONCEPTS

Today, the concept of achromatopsia as a syndrome caused by damage to cortex outside the striate area is no longer a controversial subject. Since 1973 several reports, armed with brain scans, have shown that it is the consequence of lesions in the lingual and fusiform gyri (Green and Lessell, 1977; Pearlman *et al.*, 1979; Damasio *et al.*, 1980; Heywood *et al.*, 1987; Kölmel, 1988). In all, save the 2 cases of Kölmel, the achromatopsias have had an associated disorder, either a scotoma only or a scotoma and some other disorder, such as a prosopagnosia. Yet such associated disorders have not inhibited an interpretation which supposes that achromatopsia is due to damage to a specific area of the human prestriate cortex. It is not the advent of computerized tomography that has brought about this change in interpretation, for the cortical damage revealed by such techniques is not superior to that revealed by, for example, the postmortem studies of Verrey or of Lenz. Indeed, nothing in the computerized tomograms of the brain equals the highly detailed microscopic examinations of Lenz, who nevertheless dismissed his own evidence in favour of the unsubstantiated view that the white matter must have been the causative factor (Lenz, 1921). To understand this change in the way we view evidence which, itself, has not changed much, we must look at changing concepts of vision as a process and of the role of the visual cortex in it. With the limits of the primary visual, or striate, cortex settled, the chief changes have been in the very concepts that prevented an acceptance of the earlier evidence, namely of vision as a dual process, the concept of association cortex, and the demonstration that uniform cytoarchitecture need not imply a uniform function.

The demise of the concept of the dual nature of visual processing

The multiplicity of visual areas

Perhaps one of the chief factors leading to the demise of a concept which had supposed that vision is a dual process, a concept which had been so influential in inhibiting acceptance of the evidence for achromatopsia, was the demonstration of the presence of multiple visual areas in the cortex lying outside the primary visual, or striate, area, which we may from now also call V1. This implied that vision must be a more complex

process. The evidence for the existence of obviously visual areas lying outside V1 and with well defined boundaries began with the demonstration by Clare and Bishop (1954) of a visual area in the suprasylvian sulcus of the cat. This was followed by the cytoarchitectonic studies of Otsuka and Hassler (1962) in the cat which delineated two areas, 18 and 19, later studied physiologically by Hubel and Wiesel (1965). Then came studies in the macaque (Cragg, 1969; Zeki, 1969, 1971) and the owl monkey (Allman and Kaas, 1971*a, b*) which, collectively, established the principle of the multiplicity of visual areas in the primate brain. This evidence showed that the cortex surrounding V1 is not a single and uniform field, as Lashley had supposed, or made up of two fields with indistinct boundaries, as Brodmann and others had believed. The notion that one of these areas might alone be involved as a consequence of a vascular lesion, for example, no longer seemed so fantastic.

Multiplicity of areas within a uniform cytoarchitectonic field

A conceptual limitation that was overthrown by these developments was the common supposition that an area of uniform cytoarchitecture is also one of uniform function. In the macaque monkey, anatomically and functionally distinct visual areas were found to reside in the same cytoarchitectonic area (fig. 5). For example, areas V2, V3, V3A and V4 all coexist in Brodmann's area 18, yet they differ profoundly in their functional properties (Zeki, 1978*a*). This made it unnecessary to suppose that an area that is uniform in its cytoarchitecture is also uniform in its function. This in turn created an attitude that no longer questioned the possibility that a specific defect may result from a small lesion, limited to only a small part of a relatively large cytoarchitectonic field. In the same way, the demonstration that V1 itself is not the uniform structure that its cytoarchitecture suggested it to be led scientists not to dismiss the evidence for nonoriented colour cells within it, as they had in the past, a change which led the way to a more detailed understanding of the colour pathways in the brain.

The demonstration of functional specialization in the prestriate visual cortex

It was, however, the demonstration of functional specialization in the prestriate visual cortex of the macaque monkey (Zeki, 1974*b*, 1978*a*) which, perhaps more than any other factor, led to a change in our view of vision as a dual process. Hubel and Wiesel, by restricting their stimuli largely to oriented lines, had supposed that the visual areas lying outside V1 merely continued the process of analysis which starts at the retina, generalizing over larger parts of the field of view the specification for orientation selectivity generated earlier, and then generating new specifications which were then generalized again, in a hierarchical chain. Adherence to this view of an exclusive hierarchical strategy was to confuse them when they found that most cells in the visual area defined by Clare and Bishop are directionally selective. They thought of it as executing the 'same processes' that occur in area 18 'but with different degrees of refinement', leaving them '... with the puzzling prospect of an area for which we can ... assign no obvious function' (Hubel and Wiesel, 1969). The evidence from studies of the macaque monkey prestriate cortex showed that this process of increased elaboration, underlying the hierarchical strategy, was only part of the picture. More impressive was the fact that different groups of areas are specialized to execute different

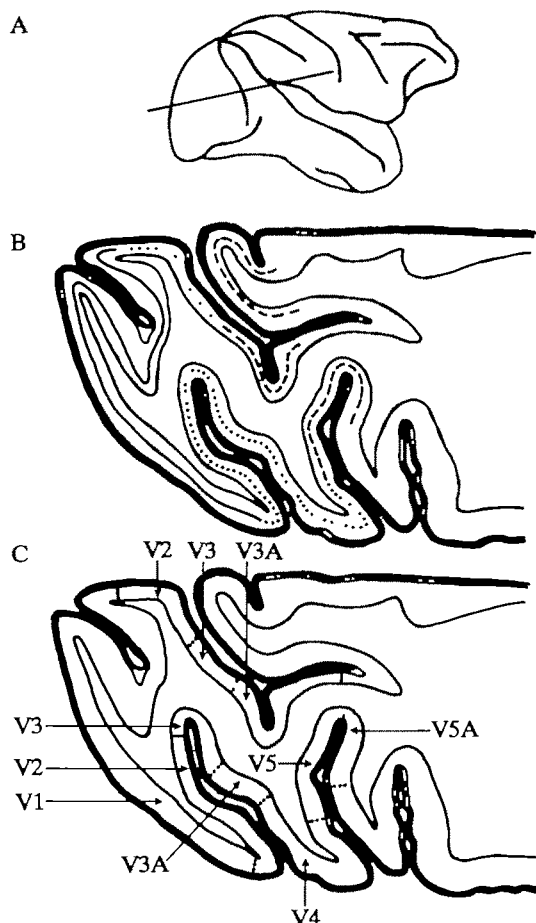


FIG. 5 Horizontal sections taken through the brain of the macaque monkey at the level shown in A. The section in B shows the extent of Brodmann's (1905) areas 18 (dots) and 19 (dashed lines). The section in C shows the visual areas within Brodmann's cytoarchitectonic subdivisions (from Zeki, 1978a). Area 17 (continuous lines)

visual functions. The first such area to be characterized was V5, lying on the posterior bank of the superior temporal sulcus, and probably functionally equivalent to the Clare-Bishop area. The cells in it are overwhelmingly direction selective and, for most, spots of light moved in the appropriate direction give the optimal response. Critically, none of the cells is wavelength selective (Zeki, 1974a; Gattass and Gross, 1981; Van Essen *et al.*, 1981; Movshon and Newsome, 1984). In contrast to the conclusions reached earlier about the Clare-Bishop area, the positive evidence (presence of directional selectivity), and the negative evidence (absence of wavelength selectivity), established at once that the area is specialized, in this case for visual motion (Zeki, 1974a). The area is therefore not involved in further processing of the information processed by antecedent areas, but in a different, and specialized, kind of processing. This was followed by the demonstration that colour and wavelength selectivity is overwhelmingly emphasized within the V4 complex of areas (Zeki, 1973, 1977; Desimone and Schein, 1987), in

distinction to V5 and also in distinction to V3 and V3A, where the majority of cells are orientation selective without being wavelength selective (Zeki, 1978c). The heavy emphasis on wavelength selectivity in V4 suggested that it is an area specialized for colour vision, while the heavy concentration of orientation selectivity within V3 and V3A suggested that these areas are more involved with form vision. Moreover, anatomical evidence showed that the prestriate visual areas are not connected exclusively serially with one another, but that each part of V1 sends parallel, and independent, outputs to different areas of the prestriate visual cortex, thus establishing the principle of parallel processing in the cerebral cortex (Zeki, 1975). Together, these findings led to a theory of functional specialization within visual cortex (Zeki, 1974b, 1978a), the term visual cortex now being used in a broader sense, to include the striate as well as the prestriate cortex. In particular, the demonstration that area V4, unlike some of the other visual areas of the prestriate cortex, is heavily involved in colour vision, made it very plausible to suppose that, in man too, such a specialization might occur, which would account for the achromatopsia following specific prestriate lesions. Verrey's evidence, and that of others, now acquired a new meaning.

Above all, this evidence showed that vision is not the dual process that Lissauer (1890) and his followers had imagined it to be. Instead, it is a complex process, involving several specialized areas and their interactions, with probably several more areas yet to be identified and charted. It also made the concept of association cortex, in the sense intended by Flechsig and Lissauer, no longer tenable. For the responses of cells in these areas suggested that they are still concerned with relatively early, though specialized, aspects of vision and not uniquely concerned with associating visual signals with other sensory signals or with past visual impressions. The limiting strait-jacket of an 'apperceptive' cortex and an 'associational' cortex, the one merely involved with the reception of visual impressions, and the other with their final elaboration, was overthrown. The new concepts of functional specialization were a good deal more hospitable to the evidence relating to achromatopsia than earlier concepts had been. For there no longer seemed anything strange or incompatible in supposing that there could be several visual areas outside the striate cortex, in the human brain, and that one of these might be specialized for colour vision or indeed for some other attribute of vision, although for a relatively recent paper denying a specialization for colour in the primate visual cortex, and questioning the role of V4 in it, reference may be made to Schein *et al.* (1982). It is not surprising to find, therefore, that the description of a specific visual defect, that of motion blindness, following a study of a single case with a lesion in prestriate cortex (Zihl *et al.*, 1983) was immediately accepted, without any of the hostility that cases of achromatopsia had generated. The climate had changed following the demonstration of functional specialization in the visual cortex of the primate brain.

Functional segregation in the striate cortex (V1)

But a mystery remained, namely the manner in which the different signals, especially the colour signals, reach V1. This was not an anatomical problem, because the anatomical results had shown that the pivotal prestriate areas concerned with motion, form and colour receive inputs directly from V1 (Cragg, 1969; Zeki, 1969), with the input to V4 being restricted to foveal V1 (Zeki, 1978b). The problem was the functional architecture of V1 itself, especially in relation to colour. The most complete and detailed

studies of V1 had reported few wavelength selective cells in it, with all cells outside layer 4C being orientation selective (Hubel and Wiesel, 1968). This seemed to be quite contrary to the speculation of Pötzl (1928), or of Halpern and Hoff (1929) or of Poppelreuter (1923), all of whom had supposed that colour must be segregated in the striate cortex and localized in its upper layers.

In addition, in the early seventies, it seemed difficult to account for the emergence of colour properties in a visual area of the prestriate cortex which is fed from a colour poor V1 (*see, e.g., Zeki, 1974b*). Because the same region of the V1 has independent and parallel projections to different prestriate visual areas, the suggestion was nevertheless made that another major function of the striate cortex, in addition to those ascribed to it by Hubel and Wiesel, must be '... to segregate out the information coming over the retinogeniculo-cortical pathways and parcel this information out to different cortical areas for further analysis' (Zeki, 1975). Towards the latter part of the seventies, anatomical and physiological evidence for such a supposition began to emerge. Lund *et al.* (1975) had injected V5 with the enzyme horseradish peroxidase and found that labelled cells in V1 are not distributed in all layers, but restricted to layer 4B and upper layer 6, thus showing that cells dealing with a particular type of signal, namely motion, are segregated in separate layers of V1. More recent evidence has shown that, even within layer 4B, cells whose axons are destined for V5 occupy separate patches from cells whose axons are destined elsewhere (Shipp and Zeki, 1989a). In terms of colour vision, Poggio *et al.* (1975) showed that, unlike what was commonly supposed until then, there are substantial numbers of wavelength selective cells in V1, that most of these are concentrated in parts of V1 representing central vision and the majority are not orientation selective. Soon thereafter, Michael (1981) found that wavelength selective cells occur in groups within V1 and that they are separated from each other by cells not selective for wavelength, although he reported both types of cell to be orientation selective. The mystery thus began gradually to be resolved, and was resolved more fully when Livingstone and Hubel (1984) and Horton (1984), using the cytochrome oxidase technique developed by Wong-Riley (1979), found that V1 is characterized by a set of darkly staining, cytochrome oxidase rich, columns extending from the surface to white matter, but especially prominent in layers 2 and 3 where they are known as the cytochrome oxidase blobs or puffs (*see fig. 6*). Recording from the upper layers of V1, Livingstone and Hubel (1984) found that most cells inside the blobs are wavelength but not orientation selective, whereas most cells outside the blobs are orientation but not wavelength selective, thus confirming further the segregatory role of V1 and modifying Hubel and Wiesel's (1977) model of V1 to include the functional segregation found within it. Such a functional segregation of form, colour and motion within V1 was a remarkable vindication of the views of Poppelreuter (1923) concerning the organization of the striate cortex, made some 60 yrs earlier.

The colour pathways in the cerebral cortex

It is likely that the kind of organization sketched above for the macaque monkey is also found in man. Indeed, as far as the organization of V1 itself is concerned, the brain of man is very similar to that of the monkey (Horton and Hedley-Whyte, 1984; Burkhalter and Bernardo, 1989). It is therefore likely that the segregated colour pathways described

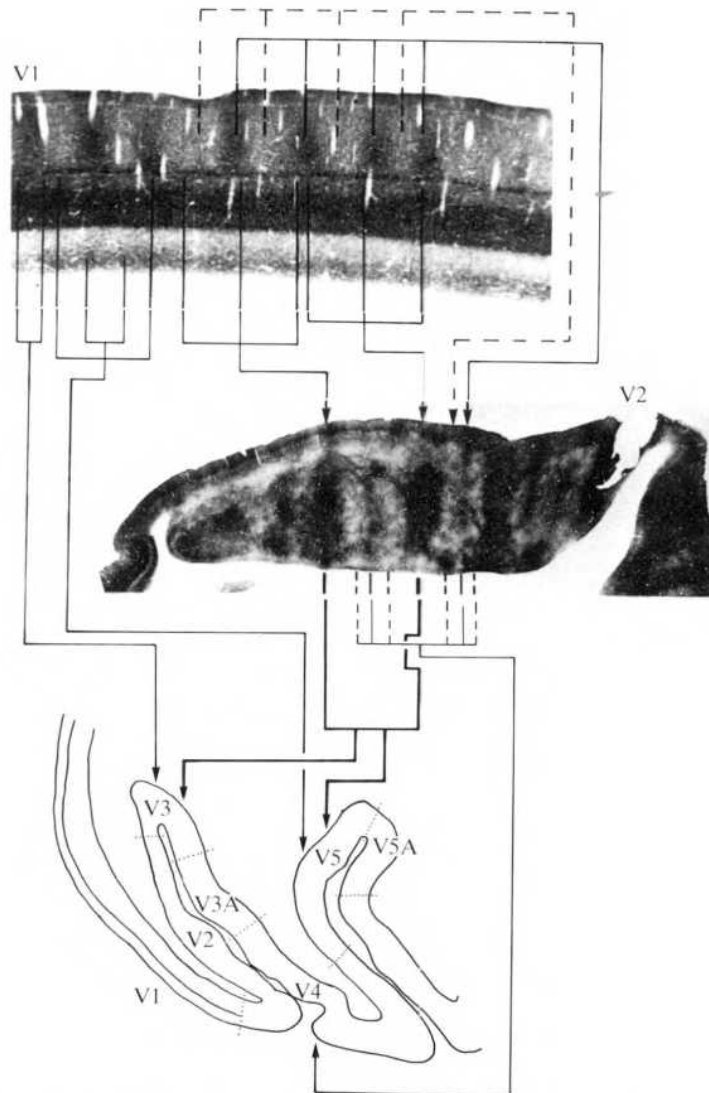


FIG. 6. Connections of areas V1 and V2 with one another and with the specialized areas of the prestriate visual cortex. The latter are shown at the bottom of the fig. in a horizontal section through the brain taken at about the same level as the sections of fig. 5. The blobs of V1, seen prominently in the upper layers of this radial section taken through it, project to the thin stripes of V2, which in turn project to V4. The interblobs of V1 project to the interstripes of V2, which also project to V4. Layer 4B of V1 projects to V5 and to V3. It also projects to the thick stripes of V2, which in turn project to V5 and to V3. The section through V2 is parallel to the cortical surface, since it is at this angle that its stripes are seen to best advantage.

below for the macaque monkey are also similar in man. This allows us to give a more detailed interpretative account of the central achromatopsias in man.

All the present evidence suggests that the pathways involved with colour vision are maintained segregated throughout much of the cortex, a finding that in itself may shed a significant light on some types of achromatopsia. Work undertaken since the

demonstration of functional specialization in the prestriate visual cortex shows that the separation of visual functions can be traced right back to the retina itself, where there are two major classes of ganglion cells, the $P\alpha$ and the $P\beta$ cells (Leventhal *et al.*, 1981; Perry *et al.*, 1984). These have different properties. The $P\alpha$ cells are indifferent to wavelength and receive additive inputs from all three cone mechanisms, or at least from the middle and long wave cones. They also have faster transient responses and faster conduction velocities. By contrast, $P\beta$ cells are wavelength selective. They receive opponent inputs from different cone mechanisms, the net result of which is to render them selective for narrower segments of the visible spectrum. They also have slower, tonic, responses (Dreher *et al.*, 1976; Schiller and Malpeli, 1978). These two types of ganglion cells project differently to the lateral geniculate nucleus, the $P\alpha$ projecting to its magnocellular (M) layers and the $P\beta$ cells to its parvocellular (P) layers, subdivisions of the nucleus with similar properties (Wiesel and Hubel, 1966). Because of this similarity, and because of the differential projection of the P and the M layers to the visual cortex, the terms P and M are more widely used today to refer to visual areas in the cortex whose input derives predominantly from one system or the other.

The P and the M system have different destinations in the visual cortex. P cells are relayed to the blobs and interblobs of layers 2 and 3, where wavelength selectivity is concentrated in the blobs, in cells which lack for the most part orientation selectivity; many have double opponent concentric receptive fields, which are well suited to extracting information about colour (Michael, 1981; Daw, 1984). Cells preferring particular wavelengths are grouped together in separate blobs (T'so and Gilbert, 1988). Orientation selectivity, by contrast, is concentrated in the interblobs, in cells which are not wavelength selective. Both double opponency and orientation selectivity are generated in the cortex itself. Thus the P system seems to split in the upper layers of V1 into two pathways, one concerned primarily with colour and another primarily with form. The M system terminates quite separately in layer 4B of V1, where again at least two new categories of cells—orientation selective cells concerned with form, and direction selective cells concerned with motion—are generated.

The striate cortex is surrounded by the second visual area, area V2, which receives a topographically organized input from V1 (Cragg, 1969; Zeki, 1969). Like V1, V2 has a characteristic pattern when stained for the metabolic enzyme cytochrome oxidase. In V2 the pattern consists of a set of thick and thin stripes which are separated from each other by interstripes, one cycle of a thin stripe, thick stripe and two interstripes occupying about 4.5 mm (Tootell *et al.*, 1983; Shipp and Zeki, 1989b) (*see fig. 6*). Most cells in the thin stripes are not orientation selective, and about 50% are wavelength selective. By contrast, cells in the thick stripes and interstripes are orientation, but not wavelength, selective. Directionally selective cells are concentrated in the thick stripes (DeYoe and Van Essen, 1985; Shipp and Zeki, 1985; Hubel and Livingstone, 1987). In other words, there is a strict functional segregation in V2, just as in V1. There is also a remarkable order in the topographic projections from V1 to V2, reflecting the specialization of the blobs and interblobs of V1 and the stripes of V2. In the P system the blobs of layers 2 and 3 of V1 project to the thin stripes of V2 and the interblobs to the interstripes. In the M system, layer 4B projects to the thick stripes. The consequence is that the thick stripes belong predominantly to the M system, whereas the thin stripes and the interstripes belong to the P system.

Both V1 and V2 are segregator areas, in that cells specialized to process different kinds of visual signals are not only segregated within them, but project in a segregated way from them to the more specialized visual areas of the prestriate cortex. V1 projects directly to V3, V5 and also to V4, although the projection to the latter area is predominantly from foveal V1 (Cragg, 1969; Zeki, 1969, 1978c). The projection to V3 and V5 is from layer 4B (Burkhalter *et al.*, 1986; Shipp and Zeki, 1989a). The precise origin of the more limited output from V1 to V4 is not certain yet, but it is likely to be from the wavelength selective blobs (Yukie and Iwai, 1985). V2 also projects to these specialized visual areas (Zeki, 1971) and its projections are equally specific: the thick stripes project to V3 and V5 and the thin stripes and interstripes project to V4 (DeYoe and Van Essen, 1985; Shipp and Zeki, 1985, 1989b; Zeki and Shipp, 1989).

From these connections, summarized in fig. 6, and from the parallel physiological evidence, it becomes evident (1) that the M system is concerned with both form and motion; (2) that the pivotal prestriate area for the motion system is V5; (3) that the pivotal prestriate area for the form pathway derived from the M system is V3 (and V3A); (4) that the P system is concerned with colour and with form in association with colour, and relays to V4; (5) that there are consequently two form systems, one derived from the P pathway and the other from the M pathway.

Area V4

It is likely that there is a colour centre in the lingual and fusiform gyri of man which is the homologue of area V4 in the macaque monkey. At least some of the characteristics of achromatopsia can be accounted for in terms of the known anatomy and physiology of V4, which is outlined below.

V4 was first defined on anatomical grounds, by virtue of the input that it receives from V2 (Zeki, 1971). Later anatomical and physiological studies showed that it stretches from the anterior bank of the lunate sulcus, where it borders V3A, to the posterior bank of the superior temporal sulcus, where it borders V5 (Zeki, 1977) (*see* fig. 5). We refer to this larger region as the V4 complex. Its dorsal and ventral limits are not precisely defined. It consists of at least 2 areas, with probable subdivisions within each. The posterior part, V4, receives its input from V2 while the anterior part, V4A, receives its input from V4 (Zeki, 1977).

The area is almost exclusively concerned with the central 30° of vision. The receptive fields of its cells are larger than those of V1 or V2 (*see* fig. 7) and its topographic organization is correspondingly cruder (Zeki, 1977; Tanaka *et al.*, 1986). This relative crudity is also reflected in its callosal connections. Unlike areas such as V1 or V2, in which the callosal fibres connect a narrow strip of cortex where the vertical meridian is represented (Whitteridge, 1965; Zeki, 1970; Zeki and Sandeman, 1976), the callosal connections of V4 are more widely distributed (Zeki, 1970; Van Essen and Zeki, 1978), itself suggestive of a less localized representation of the vertical meridian (fig. 8). Equally, it is very rich in intrinsic connections and both these features are probably of importance in its role in colour vision (*see below*). Although it is mostly the contralateral hemifield that is mapped in V4, the receptive fields of cells nevertheless not only extend to, but cross over into the ipsilateral hemifield for up to 5°. This seems to be consistent with the role of an area which, to execute its functions, must collect information from large

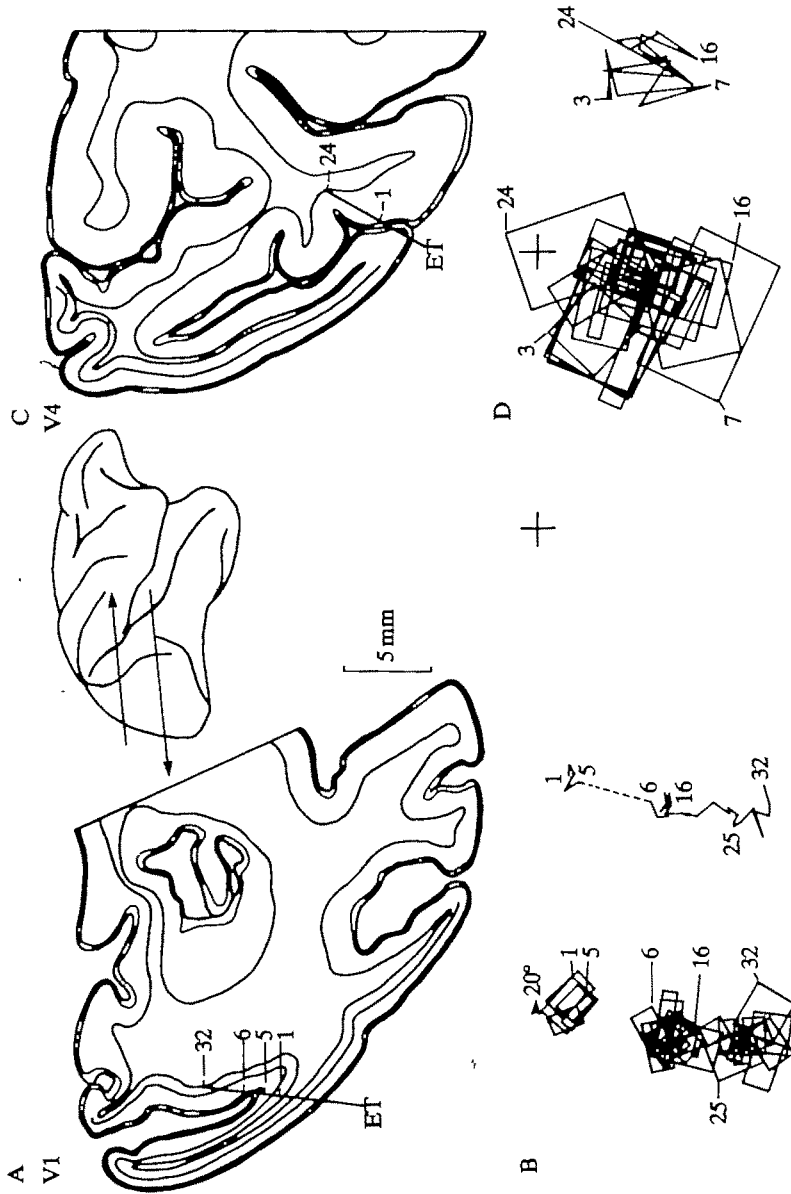


FIG 7 Reconstruction of 2 tangential penetrations, through V1 (left) and through V4 (right) to show the progression in receptive fields in the 2 areas. ET = electrode track. Note the orderly progression of receptive field positions in the penetration through V1. This is better seen in B, where the shift from the centre of one receptive field to that of the next is shown (the dashed lines indicate a gap between fields 5 and 6). By contrast, the shift is much less orderly in V4 and this can be seen more clearly in D. The crosses indicate the positions of the forcess with respect to each penetration.

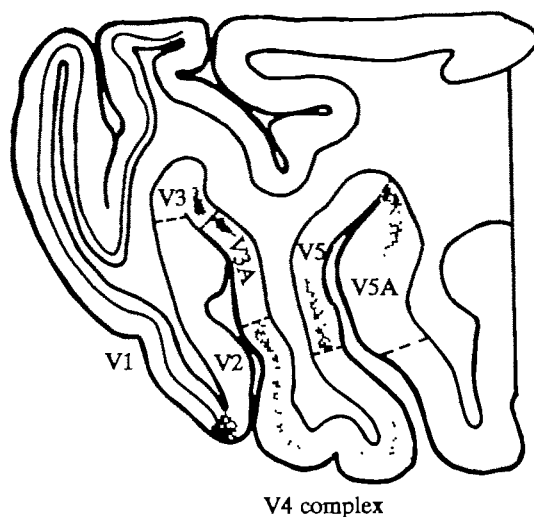


FIG. 8. Reconstruction of a section through the striate and prestriate cortex of the macaque monkey to show the distribution of the callosal fibres (stippling). Callosal fibres distribute at the V1–V2 boundary and also at the V3 and V3A boundary. But they are much more widespread within V4, reflecting its relatively crude topography

parts of the field of view. There is, indeed, evidence to suggest that the responses of cells in V4 of one hemisphere can be affected by activity in area V4 of the other hemisphere. This evidence is of interest in considering studies in man which suggest that it is areas central to V1 and V2 which are involved in the construction of colours (*see below*).

Physiologically, V4 is characterized by a heavy concentration of wavelength selective cells, even many of the orientation selective cells within it displaying some kind of wavelength selectivity, unlike their counterparts in V1 and V2 (Zeki, 1973, 1977, 1983a; Desimone and Shein, 1987). In fact, physiological and anatomical evidence suggests a certain compartmentalization within V4, with one compartment containing predominantly orientation selective cells and receiving its input from the interstripes of V2 and the other containing predominantly wavelength selective cells and receiving its input from the thin stripes of V2 (Zeki and Shipp, 1989) (fig. 9). Since most of the cells in the interstripes are not wavelength selective, it follows that wavelength selectivity is conferred on the orientation selective cells of V4 either by a convergence of inputs from the thin and interstripes of V2 or by intrinsic connections within V4 itself.

V4 and the long range processes in colour vision

Superficially at least, many of the properties of V4 seem to render it especially well suited for the purpose of constructing colours. Colour vision is a complex process in which the nervous system has to undertake an operation to compare the intensities of lights of different wavelengths reflected from one part of the field of view with those coming from surrounding parts. More compellingly than ever before, Land (1974) has shown that the colour of a surface which forms part of a complex multicoloured scene

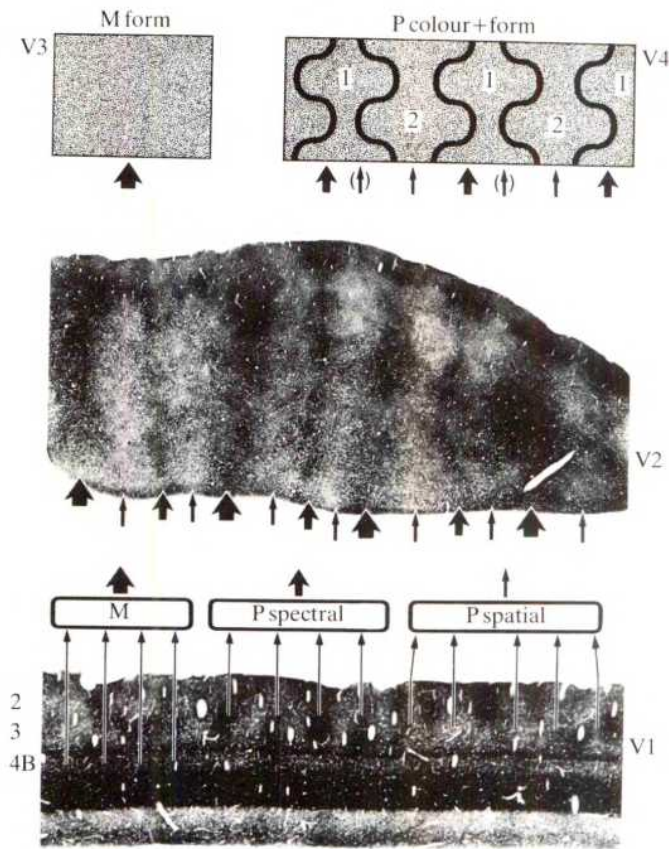


FIG. 9. Diagrammatic reconstruction of the pathways in the visual cortex to show the two *form* systems and the compartmentalization within V4. The *form* pathway derived from the M system is relayed from layer 4B of V1 to V3, directly and through the thick stripes of V2. It is not associated with colour. The P *form* pathway, associated with colour, is relayed from the interblobs of V1 to the interstripes of V2 and thence to V4. It is associated with the colour pathway, which is relayed from the blobs of V1 to the thin stripes of V2 and thence to V4. There is in addition a projection from V1 to V4, but its components are not yet clear. Anatomical and physiological evidence suggests that V4 has two sets of compartments, a Type 1 compartment receiving mainly from the thin stripes and a Type 2 compartment receiving mainly from the interstripes. The fact that most cells in V4 are wavelength selective argues for an interaction between the two compartments within V4. (From Zeki and Shipp, 1989.)

is not determined solely by the wavelength composition of the light reflected from it; it also depends on the wavelength composition of the light from surrounding areas. This accounts for the single most important property of the colour system in the brain, namely the ability to assign a constant colour to a surface in spite of differences in the illuminant in which the surface is viewed. This is because when the illuminant changes the brain is able to compare the changes in intensity of different wavelengths of light from many parts of the field of view. The process must depend upon long range interactions within the nervous system which allow a cell or a group of cells to collect information simultaneously from large parts of the field of view, a process in which V4 may play an important role by virtue of its extensive callosal and intrinsic connections. In this process of comparison, boundaries between surfaces are critical, and this may be much

aided by the presence of orientation selective cells within V4, though how orientation selective cells interact with wavelength selective cells is still unknown. The borders between surfaces are detected by comparing the intensity of light of a given waveband reflected from neighbouring points. If great, the difference is assumed to be due to points belonging to two different surfaces with different reflectances; if small, it is attributed to uneven illumination and ignored. The reflectance of a surface (i.e., the amount of light of a given waveband reflected from it, expressed as a percentage of the light incident on it) does not depend on the intensity of illumination. A surface will reflect the same percentage of light of any given wavelength no matter what the actual intensity. Different surfaces have different reflectances for light of the same waveband. Hence when multicoloured surfaces are illuminated by light of one waveband, different ones will acquire different lightnesses, on a scale from white to black, lightness being the biological correlate of reflectance (Land, 1974) (*see* fig. 10). For example, when a multicoloured scene is illuminated with long-wave light alone, areas with a high reflectance for long-wave light (white, red, yellow) will appear very light while those with a very low reflectance (black, green, blue) will appear dark. Middle-wave light will produce a different lightness record for the same scene and short-wave light will produce yet another. The lightness of an area is independent of the actual energy of the light reflected from it, but is determined by a comparison of the intensity of light reflected from it in relation to the intensity of light of the same waveband reflected from other areas. This process depends on long range interactions within the nervous system. According to Land, the colour of an area is synthesized by comparing, not mixing, the lightness of an area generated in each of at least three different wavebands (*see* fig. 10). Since the lightness of an area is independent of the actual energy of light reflected from it alone and is the result of a comparison which depends on long range interactions and since colour is a comparison of these comparisons, it follows that colour, too, depends on long range interactions and is also independent of the actual energies of light reflected from it alone. An explanation of colour vision in these terms accounts for the property of colour constancy. We emphasize here that all colours are constant colours and that the dichotomy often drawn between constant and inconstant colours is mistaken. In short, colour is generated by a complex set of specific interactions occurring within the CNS, interactions which are different from those required to generate other properties of the visual scene.

Long range interactions in man

Indirect evidence that in man, too, an area like V4, that is one in which the callosal connections are not limited to the central 1–2°, is critical for generating colours in the cerebral cortex derives from the experiments of Land *et al.* (1983). Their patient, whose corpus callosum had been split, was asked to determine the colour of a surface (which was purple) when the rest of the multicoloured display was in one or the other of his two hemifields. The separation between the fixation target (the purple surface) and the border of the multicoloured display was 3.7°. When normal subjects view such a surface in complete isolation, they report its colour to be white. If, without changing the energies of light coming from the (perceptually white) surface, the surround of the display is brought into view (even if the surround is separated from the target by 4° or more and is in the other hemifield), they report it to be purple. However, the subject

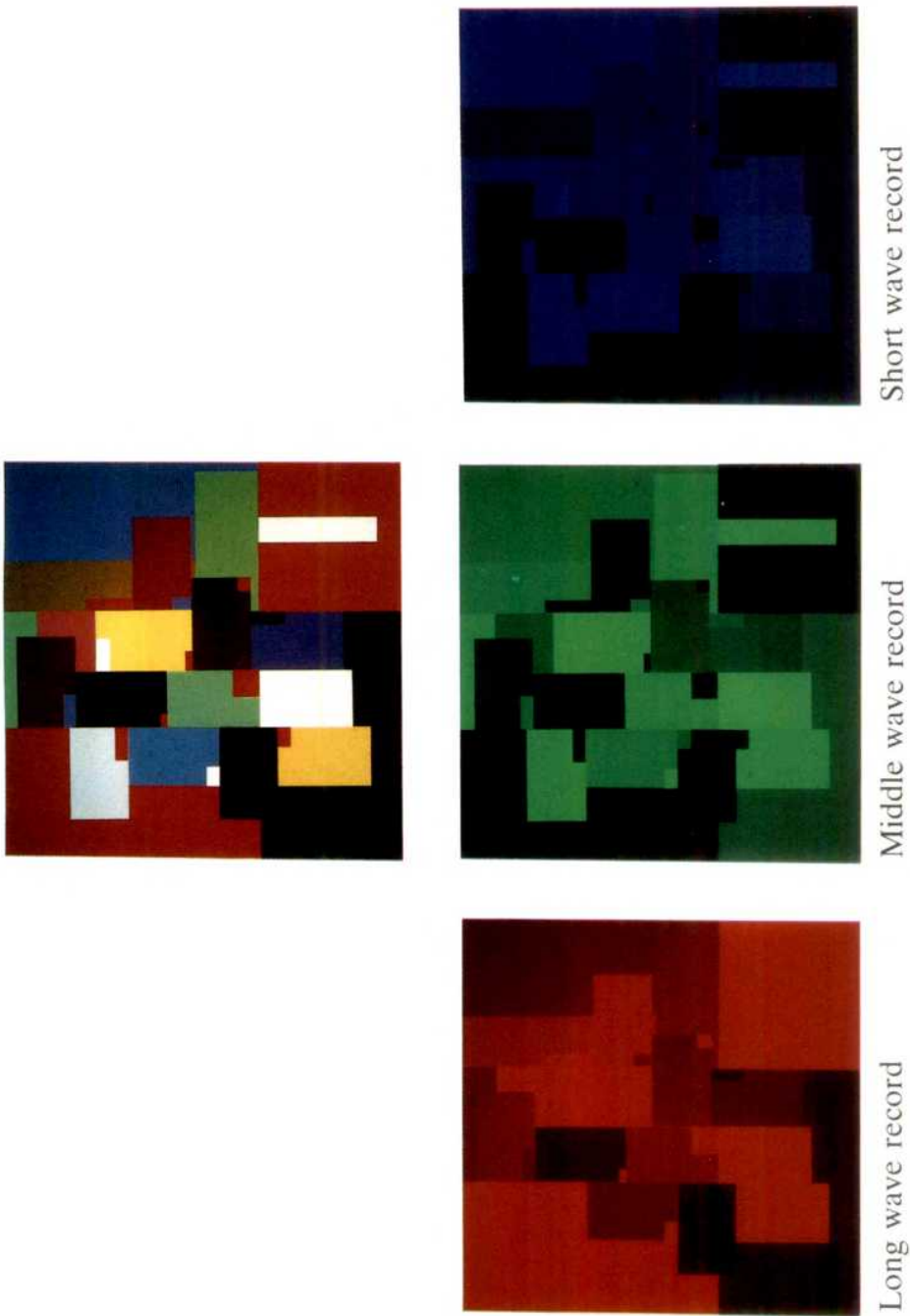


FIG. 10. A multicoloured display (*above*) and its lightness records (*below*) when it is viewed in long (*left*), middle (*centre*) and short-wave (*right*) light. See text for details.

described was not able to make the comparison when the target was presented to one hemifield and the rest of the display to the other, presumably because long range interactions across the hemispheres are not possible in the absence of callosal connections. By reference to the distribution of the callosal fibres in the macaque brain, and assuming a similarity with the human brain, it can be concluded that the synthesis of the colour (in this case purple) must occur in an area whose organization is similar to that of macaque monkey V4. The callosal connections of V1 and V2 are limited to the representation of the vertical meridian (Whitteridge, 1965; Zeki, 1970). The callosal connections of V3 and V3A are more widespread (Zeki and Sandeman, 1976; Zeki, 1977; Van Essen and Zeki, 1978), but none of these areas is concerned with colour vision. The first area concerned with colour vision and whose cells have large receptive fields which cross over into the contralateral ipsilateral hemifield by up to 5° is V4. Moreover, the relatively coarse topographic organization of V4 is reflected in callosal connections. These are much more widespread than those of V1 and V2, and are thus capable of mediating interhemispheric long range interactions between targets separated across the midline by more than 3.7° . It follows that, in man too, an area similar to V4 must be the region where colours are synthesized from such comparisons.

An interesting insight into cerebral areas involved with colour vision in man is also obtained from the patient of Ruddock (Hendricks *et al.*, 1981). A number of reasons, discussed by the authors, suggest that the severe inhibitory effect produced by red stimuli in this subject are due to central rather than peripheral abnormalities, but which central areas is problematic. The fact that the inhibition spreads across the midline over about 4° into the contralateral hemifield, suggests that the earliest possible site for the inhibitory spread must be V4 although it is possible, as the authors themselves suggest, that areas central to V4 may be involved.

The physiology of the colour pathways

The long range interactions present in topographically well organized areas such as V1 and V2, as judged by the horizontal spread of axons within the cortex following punctate lesions, are somewhat limited (Fisken *et al.*, 1975; Rockland and Lund, 1983). By contrast, the lateral spread of intrinsic connections within V4 is extensive. In addition, the much coarser topography within it suggests that cells in V4 are better suited to the collection of information from larger parts of the field of view. Correspondingly, physiological results suggest that the responses of some, at least, of the cells in V4 correlate with the human perception of colours whereas those in V1, and possibly V2, do not (Zeki, 1983*b*). Thus a straightforward, long-wave selective cell in V1, for example, will respond to a surface of any colour if that surface is reflecting an excess of long-wave light, compared with light of other wavelengths (fig. 11). Equally, a long-wave ON, middle-wave OFF cell in V1 might be made to give an ON or an OFF response to an area of any colour by the simple expedient of varying the relative amounts of long and middle-wave lights reflected from it, without changing its colour (Zeki, 1983*b*). The double opponent cells in V1, and possibly in V2, may correspond to an initial wavelength differencing stage, whereby a cell can compare the reflected intensity of light of a given waveband reflected from the centre of the receptive field with the intensity of light of the same waveband reflected from the surround (Zeki, 1985), a process that is critical

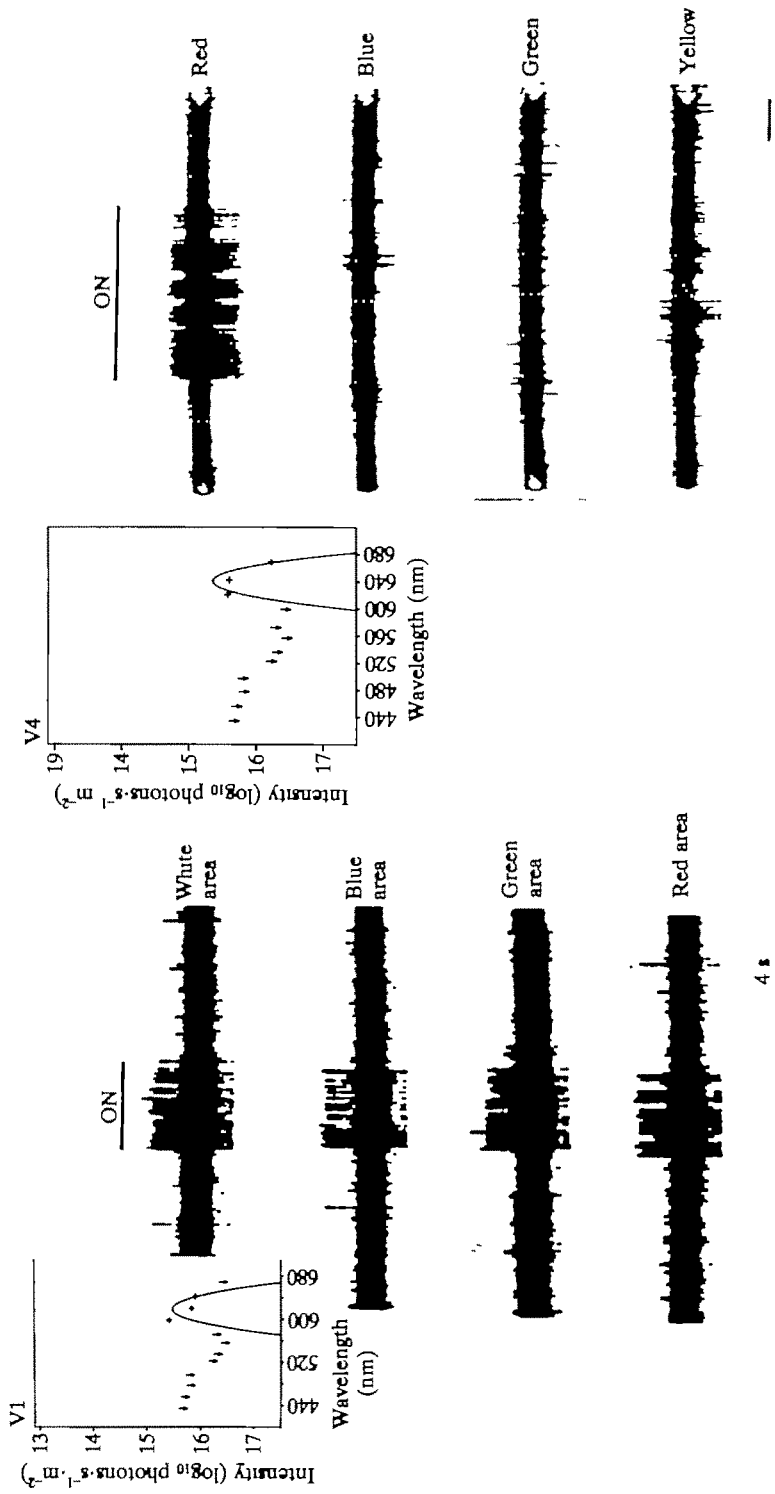


FIG. 11. The responses of a long-wave selective cell in V1 (*left*) and in V4 (*right*) to various areas of a multicoloured display. When each area of the multicoloured display was put in the receptive field of the cell, it was made to reflect the same triplet of energies. The V1 cell responded to each area of the display regardless of its colour, whereas the V4 cell responded to the red area alone. Insets show the wavelength sensitivity curves of the cells (From Zeki, 1983a.)

in generating colours (Land, 1974) since when the illuminant in which a scene is viewed is changed, the wavelength composition of light coming from all parts changes. By contrast, at least some cells in V4 have responses which are, within wide limits, independent of the relative amounts of light of different wavebands reflected from their receptive fields and which therefore correlate with the human perception of colours (Zeki, 1983*b*) (see fig. 11).

This organization suggests a hierarchy in the processing of signals related to wavelength and in the generation of colour, with areas V1 and V2 registering the presence and intensity of lights of different wavelengths, and possibly undertaking a wavelength differencing operation. This process is probably continued and elaborated in V4. At any rate, the results suggest that in man, too, there must be several stages involved in the synthesis of colour, spread across at least three areas. If so, then this would provide that simple and fundamental missing link which the early neurologists could just not understand, because of the dominating position of their concepts—namely that there may be more than one cortical area involved with colour vision.

The colour pathways in the cerebral cortex of man

We have tested such a notion directly in man with the technique of positron emission tomography (PET) which measures the increase in blood flow through active regions of the brain. The results, described elsewhere (Lueck *et al.*, 1989), show that when a normal human subject views a multicoloured abstract display (a Land Colour Mondrian), there are two regions of heightened activity, one situated in the striate cortex and another in the lingual and fusiform gyri. The former may include area V2, since the resolution on such scans did not allow a convincing separation between V1 and V2. On the other hand, when the human subject views the same display, but in shades of grey which are equiluminous with their coloured counterparts, the activity in V1 remains about the same, but that in V4 falls by about one-third. This finding can be accounted for by direct reference to the known physiology of the colour pathways, described above. Many wavelength selective cells in V1 respond to a surface of any colour if it is reflecting a sufficient amount of light of their preferred wavelength. With the grey display, all 3 TV phosphors are active. Consequently, many of the wavelength selective cells in V1 will respond if there is a sufficient amount of light of their preferred wavelength reaching the eye. The same cells will naturally respond with equal vigour if the display is coloured, since each will now be activated by its own preferred wavelength. Hence the observation that the level of activity in V1, as measured by the change in blood flow, is very similar whether a grey or a coloured Mondrian is used. With the human homologue of V4, in the lingual and fusiform gyri, the situation is different. Here many cells are selective for colour rather than wavelength, in the sense that their responses correlate with the human perception of colours. They will not be active during the grey stimulation but will respond when their preferred colours are present. Since colour is a comparison of at least 3 grey level records, it follows that with the grey Mondrian the colour cells would not have been stimulated, although their precursors would have. In sum, the evidence suggests that, in man as in monkey, colour vision involves areas besides the striate cortex (and V2), and that the colour centre in the prestriate cortex is located in the lingual and fusiform gyri.

In view of the overwhelming clinical evidence suggesting that the location of the colour centre outside V1 is in the lingual and fusiform gyri, these results are naturally satisfying. Further evidence that this is a distinct region, with special visual functions, was obtained when we performed control experiments and asked subjects to view a pattern of moving black-and-white random dots. With such a stimulus, the increased activity occurred in the temporo-parieto-occipital pit, in a region corresponding to area V5 in man (Cunningham *et al.*, 1990). This constitutes the first direct evidence for a functional specialization in the visual cortex of man.

There was nevertheless an element of surprise in the results, in that there was no reliable increase in activity in the inferior temporal cortex, which might have been expected, given that V4 projects there in the monkey (Desimone *et al.*, 1980; Fries and Zeki, 1983). It is possible that inferior temporal cortex deals with even more complex aspects of colour vision, such as colour memory, and the colour displays that we employed did not activate this cortex precisely because they were specifically designed to avoid the use of memory, learning and experience (Land, 1974). Another somewhat surprising result was the lateralization, with the lingual and fusiform gyri of one hemisphere in each subject being more active than their counterparts in the other hemisphere, regardless of handedness. Such a lateralization cannot be accounted for in terms of the clinical evidence relating to achromatopsia.

In summary, the experimental evidence reviewed above shows that in man, as in monkeys, there are specific pathways dealing with colour vision.

4. A REINTERPRETATION OF THE ACHROMATOPSIAS

Armed with this new knowledge, we may now reassess the published cases of achromatopsia. We begin by emphasizing that, in the light of functional specialization in the visual cortex, there is nothing implausible about the syndrome of acquired central achromatopsia resulting from a specific cortical lesion. Since the different, functionally specialized, visual areas are geographically separate in the cortex, it is reasonable to suppose that a lesion of vascular or other origin may selectively affect a given specialized area, leading in turn to a selective impairment in vision. Indeed, given the segregation of pathways dealing with different visual signals and their association with cortical zones of different metabolic activity, it is equally plausible that, because of differential susceptibility to, say, drugs or metabolic agents, a segregated pathway may be selectively affected in the absence of a lesion. Such cases have been described. But an adequate interpretation has not been possible in the past. The new information allows us to account for some of the characteristics of achromatopsia in anatomical and physiological terms. Other characteristics can also be interpreted in the light of this evidence, although in a more conjectural way. This is nevertheless worth trying.

The pathology of achromatopsia

The relationship of the size of the lesion to achromatopsia is straightforward. Where a lesion is large enough to involve V4 in man (in the lingual and fusiform gyri) as well as V1, it will lead to achromatopsia associated with a scotoma. This is true of most cases of achromatopsia. Because the lingual and fusiform gyri border the lower lip of

the calcarine sulcus, the scotoma, when present, always involves the upper visual fields. But it can be more extensive and involve the upper lip of the calcarine sulcus and therefore the lower visual fields as well. The extent to which area V2 in the human may also be involved, and contribute to the scotoma, is not clear. As in the monkey, it is presumed that area V2 surrounds V1 and is in topographic relation to it and, moreover, that V2 is not coextensive with area 18 of Brodmann but occupies only a part of it, as in the macaque (Zeki, 1969, 1978a). Finally, it is supposed that it is interposed between V1 and the homologue of V4 in man (Zeki, 1971). It should therefore lie in the lingual gyrus and is likely to have been involved in many of the lesions affecting the lingual and fusiform gyri which invade the lower lip of the calcarine sulcus. But whether lesions in V2 produce scotomas is not known. No lesions restricted to V2 have ever been described in man and the contribution of damage to V2 to the presence, and severity, of the scotomas is not yet clear.

If the lesion is more widespread anteriorly within the fusiform gyrus, it will also lead to a prosopagnosia, a common finding. Where the lesion is restricted to area V4 within the fusiform gyrus, the consequence is an achromatopsia uncontaminated by a scotoma (Kölmel, 1988). Where the lesion is unilateral, the result is a hemiachromatopsia. The latter can be accounted for by studying the nature of visual field representation in V4 of the macaque. Physiological mapping experiments show that it is the contralateral half of the field of view that is represented in each hemisphere, even though the receptive fields of cells cross the midline by up to 5° (Zeki, 1977; Van Essen and Zeki, 1978). Such an organization in an area specialized for colour would naturally be expected to lead to hemiachromatopsia following total, but unilateral, lesions of it. That this happens in man (e.g., the cases of Verrey, 1888, and of Damasio *et al.*, 1980) confirms further the close similarity in the organization of the colour pathways in man and the macaque monkey. However, since receptive fields cross the midline by about 5° , the intact and hemiachromatopsic fields would be expected to spread across the midline to some extent. This question has not been specifically addressed in such patients.

The nature of field representation within V4 of the macaque also helps to explain why achromatopsia always involves the whole of the visual field and never just a small segment of it. Even though it is a complex of areas, V4 is much smaller than V1 or V2. Hence a lesion of a given size will compromise a far greater amount of V4 than it would of V1. Moreover, the representation of the upper and lower fields are well separated in V1, in the two surfaces of the calcarine sulcus. A lesion limited to one surface of the sulcus will therefore only result in a corresponding scotoma limited to a certain part of the field of view. By contrast, field separation is not nearly so clear cut in V4, with its much eroded topography. A lesion of equivalent size will therefore involve a greater extent of V4, both in terms of the extent of the area destroyed and in terms of topographic representation which, in V4, is limited to the central $30-40^\circ$ of visual field. This accounts for why the achromatopsia is not scotomatous in nature and always involves central fields. Given the relative lack of topographic organization of V4, and the substantial overlap of receptive fields within it, it would be expected that any partial lesion of its homologue in man might still leave a patient with some colour capacity. The fact that in most achromatopsic patients the defect is so total would argue for fairly substantial lesions of the homologue of V4. There is, however, no knowledge of the precise limits of the colour centre in the fusiform and lingual gyri

of man, and the extent of the damage in relation to the total extent of the centre has therefore never been charted.

In some achromatopsic patients the perception of some colours, usually the reds, is relatively unimpaired (Meadows, 1974a), a condition which we refer to as incomplete achromatopsia. The pathology of this condition is not certain; it may be caused by an incomplete lesion of the colour centre. Nor is it known why the perception of blues and greens suffers more. The temptation is to correlate it with the well-established fact that long-wave selective cells constitute the greater majority of wavelength selective cells in the visual cortex, both in V1 and in V4. Needless to say, in any incomplete cortical damage, the ratio of surviving long-wave selective cells, compared to middle and short-wave ones, will remain the same. To account for the relative sparing of the discrimination of reds, it might therefore be postulated that a critical mass of wavelength selective cells is required to generate the appropriate lightness record from which colour can be derived.

The role of V1 in achromatopsia

Some patients with an intact central visual field but with a lesion in the lingual and fusiform gyri are completely achromatopsic while others suffer from an incomplete achromatopsia. This creates a problem of interpretation, which includes an assessment of the role of V1 in colour vision.

Achromatopsia with intact central visual fields

Given the presence of wavelength selective cells in V1 and in V2, and given their heavy concentration in regions of central representation within those areas (Poggio *et al.*, 1975; Zeki, 1983a), it might be supposed that colour vision would be relatively unimpaired. This suggests that wavelength selective cells of V1 and V2 are not capable of mediating colour perception by themselves. A possible explanation for this may be found in studies of the physiological properties of cells in the colour pathways of the cerebral cortex. This evidence, reviewed above, suggests that the wavelength selective cells of V1 respond to wavelengths alone, and that their responses do not correlate with colours. If the same is true in man, then the wavelength selective cells of V1, even if intact in patients with a damaged lingual and fusiform gyri, would not be able to synthesize the colour of an area from the information that they receive (but *see below*). A more central area, in which cells are able to collect information from larger parts of the field of view, is required.

Residual colour vision following incomplete lesions

Where the lesion in the lingual and fusiform gyri is incomplete, V1 cells may nevertheless play their role in colour vision. The most interesting study in this regard is that of Victor *et al.* (1989). Their patient was severely impaired in his perception of blues and greens and less so of reds, following a cerebral vascular accident which involved the occipitotemporal region and thus presumably the lingual and fusiform gyri, more extensively on the left. In spite of a severe disturbance in the Farnsworth Munsell 100 Hue Test, he was nevertheless able to identify correctly the figures on 8 out of 9 Ishihara plates. Equally, his chromatic contrast sensitivity function, studied with a

static horizontal sine-wave grating, was normal, suggesting that he was able to identify differences on the basis of wavelength alone.

One explanation for this might be to suppose that the wavelength selective cells in the striate cortex mediated this performance. There are problems with this assumption chiefly because other patients with intact central visual fields are not able to distinguish colours at all. Another interpretation is that a critical mass of long-wave selective cells is able to provide an incompletely destroyed colour centre with a long-wave record, whereas the middle and short-wave systems, lacking that critical mass, are unable to provide the colour centre with their respective records of the same scene. In such a system precisely the kind of results reported in the paper would be expected, namely an ability to detect most of the Ishihara plates, using the long-wave record alone, and an inability to detect them using the middle-wave system. This can be verified by viewing the Ishihara plates through bandpass long and middle-wave filters. This would also account for the ability to detect the colour of red and yellow objects but not blue and green ones. Moreover, with a long-wave lightness record operating normally, there would be no difficulty in detecting a red-green chromatic grating, as reported.

It is interesting to note that the patient of Pearlman *et al.* (1979) shared two characteristics with this patient, a greater loss for blue and green, together with a relative sparing for the perception of reds, and an inability to recognize the letters on most of the Ishihara tests correctly. By contrast, a patient such as ours (Sacks *et al.*, 1988) or that of Young *et al.* (1980) or of Young and Fishman (1980), whose achromatopsias were more complete and who were defective for all colours, failed to identify the Ishihara tests (except for the first, demonstration, plate). It would thus seem that the Ishihara tests are of good diagnostic value in distinguishing two types of achromatopsia, complete and incomplete, whereas the Farnsworth-Munsell 100 Hue Test is not. If one lightness alone is operating, then subjects would encounter considerable difficulty in ranking the different chips, a point that can readily be verified by trying to rank the test chips through one bandpass filter or another.

Vulnerability and resistance of the colour pathways

More difficult to interpret in pathological terms are cases of achromatopsia without a scotoma and without any obvious lesion in the brain, as in the case of Sacks *et al.* (1988). Here the absence of lesions in brain scans makes it plausible to suppose that other factors may be at work. Given the purity of the syndrome, a predominant or even exclusive involvement of the colour pathways is suspected, as might happen if, for example, the cytochrome oxidase rich blobs of V1 were more vulnerable to a reduction in blood supply. If they are compromised, then the entire colour pathway leading from V1 to the homologue of V4 in man would also be compromised.

Transient achromatopsia

There is in fact an interesting report of a transient achromatopsia related to vascular insufficiency where the loss of vision, limited to the perception of colours, was usually accompanied by falling attacks (Lapresle *et al.*, 1977). The conjunction of such attacks with a cerebellar symptomatology led the authors to postulate a vascular disorder in the vertebrobasilar system, from which the posterior cerebral artery, supplying the

occipital poles, is derived. One way of interpreting transient achromatopsia is to suppose that it is due to a temporary, but partial, decrease in blood flow, to which the blobs of V1 may be particularly sensitive.

Such an explanation is naturally based on speculation and there are arguments against it. Chief of these is that the metabolically highly active layer 4C, which receives the predominant afferents from the lateral geniculate nucleus, should also be affected, leading to a more pronounced visual deficit. Metabolically more active regions of the brain are more vascularized (Harper and McCulloch, 1985) and it is possible that layer 4C has a richer blood supply, thus cushioning it from the effects of disruption. Unfortunately, information on the relative richness of the blood supply to these different layers is not available, and the suggestion must remain conjectural. But taken in conjunction with the consequences of carbon monoxide poisoning, described below, a specific involvement or sparing of the colour pathways, for whatever reason, must be considered as a possibility in interpreting the achromatopsias where there is no evidence of an anatomical lesion in the brain and where there is no accompanying scotoma.

The dissociation of colour in cases of carbon monoxide poisoning

It is interesting to consider here a peculiar phenomenon, first noted by Wechsler (1933), that carbon monoxide poisoning, while having a catastrophic effect on form and depth vision, can affect colour vision much less severely or not at all. Wechsler's results are partly compromised by the fact that his subject, a 12-yr-old boy of high intelligence, had, after the poisoning episode, a profound diminution in intelligence, suggesting a very widespread cortical involvement. Nevertheless, in his visual capacities he was severely affected in form and depth perception, and even in the perception of movements (which he later recovered slightly). But his colour vision suffered only relatively mildly. Similar results have since been recorded by Adler (1944, 1950), Hécaen *et al.* (1957) and Benson and Greenberg (1969). Adler's patient was only able to recognize objects by their colour in the early posttraumatic stages, distinguishing nurses 'by their white uniforms'. The patient of Benson and Greenberg (1969) was able to identify wavelength differences of 7–10 nm. The correct identification of colour appeared to confuse him, as when he identified a letter against a blue background as a 'beach scene' because of the blue background which he mistook to be 'the ocean'. Another patient is that of Newman *et al.* (1984) who had severe visual disturbances following a hypoxic episode. The consequence of this was that she was left completely blind in her lower fields and with form but not colour blindness in the upper fields. Although there was an extensive infarct, the cortical lesion spared the lingual and fusiform gyri. All these patients suffered from disturbances in the appreciation of forms, depths and faces, but not in colour vision, and none had a scotoma. In a sense, therefore, these patients are the reverse of the achromatopsic patients, being unable to identify objects because colour is the only clue available.

An initial reaction would be to suppose that the blobs may have been selectively spared during the hypoxic episodes, which may have affected the upper calcarine cortex more substantially. This would be so if the blobs, being metabolically more active, have a richer blood supply, thus cushioning them from the effects of the hypoxia. Whether this is so is not known. Moreover, there is an apparent contradiction between such an explanation and the explanation for transient achromatopsia given above, which supposes

that the blobs are more vulnerable to a reduction in blood supply. It is not at present easy to account for this contradiction in terms of the known organization of the colour pathways or vascular physiology. The resolution, if any, might depend upon the different consequences of oxygen depletion by reduced blood flow and carboxaemia. But between them, these results show that a pathway dealing with a specific visual submodality may be selectively affected or spared in its entirety.

Inhibitory achromatopsia

While there are several features of achromatopsia which are uniform from patient to patient and can be accounted for by the known anatomy and physiology of the colour pathways in the cerebral cortex, an interesting patient, whose case presents a challenge for interpretation of central colour vision abnormalities, is that of Ruddock (Hendricks *et al.*, 1981). The patient's abnormality manifests itself as a spreading inhibition whenever red appears in his field of view and, to a far lesser extent, the same is also observed with blue and green. The inhibition spreads for about 4° from the edge of the red surface or object and creates a kind of dynamic scotoma, so that the patient is unable to see the shape of objects or their movement in the scotomatous field. I have had occasion to examine this patient. Detailed testing showed that the inhibition was not due to the presence of long-wave light as such, since it was not there when a black, white and grey scene was illuminated with 3 projectors, 1 of which passed long-wave light only. On the other hand, whenever a red or orange surface was present in a scene illuminated with the same projectors, the inhibition manifested itself instantly. This, together with the detailed studies of Ruddock and his colleagues, suggests very strongly that the inhibition is of central origin. Since the effects are also obtained with dichoptic stimulation, it follows that the site of inhibition must be central to V1, where there are strong monocular dominances. Since the inhibition spreads for at least 4° across the vertical meridian, it also follows that the inhibition must be central to V2, whose callosal connections are limited to the central $1-2^\circ$. V4 seems likely to be the first possible site of such an inhibition, but the authors themselves suggest that it could be in even more central areas.

Whatever the causative factor, it implies a summative interaction between regions of the cortex where there are heavy concentrations of cells coding for particular colours, or wavelengths, and inhibitory connections that spread from them to regions where there are orientation and direction selective cells. The fact that the subject is able to distinguish depths in red-green random dot stereograms, although he cannot see the red dot stereogram, implies that the form-from-stereo mechanism in his cortex is immune from these inhibitory connections. At present all the evidence suggests that the connections in V1, in V2, and between them, are highly specific. Blobs connect preferentially with other blobs and avoid the interblobs, blobs of V1 connect with the thin stripes of V2 and the interblobs with the interstripes, while layer 4B projects to the thick stripes of V2 and to V3 (Livingstone and Hubel, 1984; Shipp and Zeki, 1985; Burkhalter *et al.*, 1986). The effect may be due to the back projection from V4 to V2, which is less specific than the forward projection and invades the territory of the thick stripes, as well as that of the thin stripes and interstripes (Zeki and Shipp, 1988). The difficulty with this interpretation is that it does not account for the contralateral spread across the callosum,

since the interhemispheric connections of V2 are somewhat limited to the representation of the vertical meridian and do not connect regions where eccentricities of 4° or more are represented. Although the great majority of cells in V4 are wavelength selective, there appears nevertheless to be a compartmentalization within V4, between regions where cells are predominantly orientation selective and those where they are predominantly wavelength selective (Zeki and Shipp, 1989). The lateral connections within V4 are very extensive and some form of inhibition occurring at this level and interfering with the perception of forms is conceivable. But the complete form scotoma observed in the presence of red would require that the other form system, derived from the M pathway and for which V3 and V3A are pivotal prestriate areas, should also be inactivated (Zeki and Shipp, 1988). Moreover, an interpretation in terms of V4 alone would be at odds with the syndrome in other achromatopsic patients, who are nevertheless able to see forms in spite of the fact that their colour vision is severely compromised. Thus the most plausible explanation presently available to account for this highly interesting case of disturbed colour perception is to suppose that there is a substantial abnormality in the connectivity of the cortex in this patient, with the functional subgroupings which are separate in the normal subject apparently extensively interconnected. But there is no known precedent with which to compare this patient, nor is there any model which would describe his peculiar defect.

The dissociation of form and colour in achromatopsia

The pattern of connections between V2 and V4 suggests that information on both form and colour must reach V4, and this is reflected physiologically in the fact that orientation selective cells are also found in V4 (Zeki, 1975, 1983b; Desimone and Schein, 1987). But the great majority of cells in V4, whether orientation selective or not, are also wavelength selective to varying degrees. The association of orientation with wavelength selectivity is not surprising because form (or, at least, boundary detection) is essential in the determination of colour (*see below*, and Krauskopf, 1963; Land and MacCann, 1971; Land, 1974). But this conjunction creates a problem for the interpretation of the achromatopsias.

While in many cases of achromatopsia there is a reduction in form acuity, there are nevertheless cases in which the form sense is apparently very mildly affected or not affected at all (e.g., Kölmel, 1988; Sacks *et al.*, 1988). Indeed, it is because of the relative sparing of the form system in cases where colour vision was severely compromised that the syndrome of achromatopsia was described at all. If the homologue of V4 in man is anything like that of the monkey, it would be expected to receive an input from the thin stripes as well as the interstripes of V2, that is, from both the form and colour subdivisions of the P system. Correspondingly, a disturbance of the form and the colour systems would be expected. But this is not the observed result.

One way of accounting for these observations is to suppose that such patients use the other form system, derived from the M pathway and based on areas V3 and V3A. That system is more involved with dynamic form, because of the transient characteristics of its cellular responses (Zeki and Shipp, 1988). Correspondingly, such patients would be expected to be better able to appreciate forms when they are not stationary. Unfortunately this has not been specifically and systematically tested in achromatopsic

patients, although the description of a case of visual agnosia suggests that the patient was able to discriminate the shapes of moving stimuli well, while he could only discriminate them poorly when static (Botez and Serbănescu, 1967). But in support of the suggestion is the observation that other visual functions derived from the M system—distance, depth, motion—are little affected in such patients. The other way of accounting for these observations is to suppose that the form component of the P system (i.e., the interblob-interstripe system) is diverted to an area other than the homologue of V4 in man, with the consequence that the form component of the P system is not disturbed. It would imply, in short, that the organization of the vision pathways in man is different from that of the monkey, a suggestion for which there is no evidence. But whether form perception in achromatopsia is mediated by visual areas that derive their input from the predominantly 'colour blind' M system or the 'colour blind' portion of the P system, we can account for how patients see the world in shades of grey.

The greys of achromatopsia

It is a finding repeated with almost monotonous regularity that achromatopsic patients describe the world in terms of grey and, as far as the papers under review are concerned, there is no exception to this rule. So common is this finding that it may be taken to be one of the few, perhaps the only, aspect of achromatopsia which has not generated any disagreement. Its very prevalence makes one wonder whether it does not represent the unmasking of a basic physiological stage in the processes leading to full colour vision. We may thus begin by asking whether there is any similar phenomenon demonstrable in perceptual experiments in colour vision.

When a multicoloured display is viewed in light of one waveband alone, for example, long-wave light, the various areas will appear to differ from each other in lightness alone (fig. 8). When viewed in light of another waveband, they will assume a different lightness. Land (1974) supposes that the colour of an area in a multicoloured scene is synthesized by a comparison of the lightness of an area produced in each of at least 3 wavebands. Now consider what would happen if the visual system has to operate using one lightness record alone—all the colours will be seen in different shades of grey only, which is precisely what is reported by achromatopsic patients.

Yet there is no evidence that achromatopsic patients lose 2 of the 3 pigments in the eye. On the contrary, detailed studies such as those of Mollon *et al.* (1980) show that all 3 retinal cone mechanisms are intact in such patients. Moreover, the patient of Sacks *et al.* (1988) was not only able to grade the lightness correctly when he viewed a multicoloured display in light of 1 waveband, but was also able correctly to regrade the lightnesses when he viewed the same display in light of another waveband. Finally, and significantly, when asked to compare the multicoloured Mondrian illuminated in long, middle or short-wave light alone, with the Mondrian illuminated in light of all wavebands, he reported that the latter was similar to the Mondrian viewed in middle-wave light alone, but dissimilar to the other 2. Equally, a grey level Mondrian, constructed to approximate as nearly as possible to the greys which each area would assume when the multicoloured display is viewed by normals in middle-wave light alone, was considered to be similar to the multicoloured Mondrian, but quite dissimilar to the grey level produced by viewing the multicoloured Mondrian in long or short-wave light.

This suggests that in his 'normal' viewing, the patient is using a single mechanism more closely similar to the middle-wave system. In fact, there is no need to postulate 3 separate mechanisms for generating different lightness records when the same scene is viewed in lights of different wavebands. One broad band mechanism suffices. If achromatopsic patients rely on the M system to detect form, then they must be using a system which is not wavelength selective but which receives additive inputs from all 3 cone mechanisms. In short, it must be a system with a broad spectral curve and not the narrow spectral curves found in the chromatic, P, system. Using a broad system, would the world also be seen in shades of grey and, moreover, would such patients be able to detect changes in lightness when the scene is viewed in lights of different wavebands?

Consider curves such as those shown in fig. 12, which are representative broad spectral

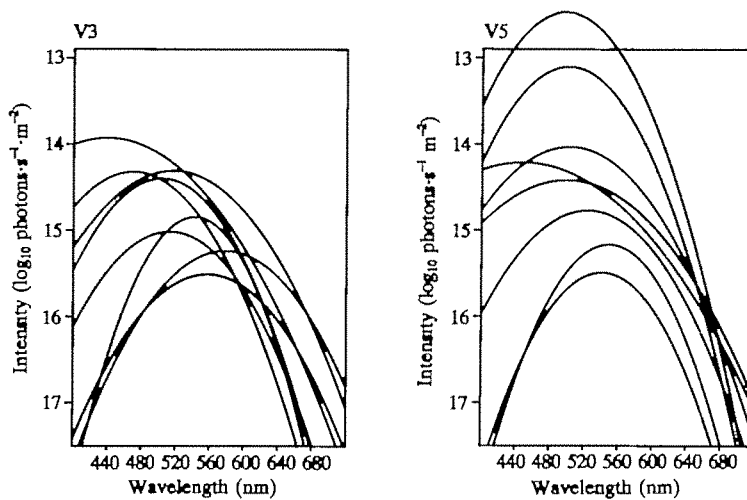


FIG. 12. The wavelength sensitivity curves (action spectra) of cells in areas V3 and V5.

sensitivity curves of cells in areas V5 and V3, which receive their predominant inputs from the M system. If, using such a broad band system, a multicoloured scene is viewed in long-wave light alone, areas which have a high reflectance for it will reflect more long-wave light and will therefore appear light. Areas which have a low reflectance for long-wave light will appear dark. When the scene is viewed in middle-wave light alone or in short-wave light alone, the same thing will happen and the system will be able to record a change in lightness. When the scene is viewed in broad band light, containing all wavebands, areas which have a high reflectance for middle-wave light will appear as the lightest, because the peak spectral sensitivity of the system falls in the 510 nm range, that is in the range of middle-wave light. Hence the system is most sensitive to this light. The light reflected from red and orange areas, being predominantly long-wave light, will be less efficient in activating the system, which is less sensitive to lights of these wavebands. Hence these areas will appear darker. In short, with a system whose spectral sensitivity is similar to that illustrated in fig. 12 the world should

be seen in different shades of grey, and this lightness record should be similar to the lightness record of the same scene when it is viewed in middle-wave light alone, precisely what we observed. This adds further to the evidence suggesting that achromatopsic patients may use the M system to detect form. The interpretation is not straightforward, however, because despite cells in V3 and V5 having broad spectral curves, their peak sensitivities do not all fall in the same spectral region, although the average peak sensitivity is 517 nm and the average bandwidth at half maximum sensitivity is about 120 nm (Zeki, unpublished results). It is possible that the dominant lightness is determined by the pooled spectral sensitivities of the cells in the areas receiving their predominant inputs from the M pathways. It is, however, also possible that, if the interblob-interstripe P system is used, the narrower spectral curves of the P cells are added together to give more central cells with a peak dominant wavelength. Determining which system is used to detect forms in achromatopsic patients remains an unsolved problem.

CONCLUSIONS

The history of cerebral achromatopsia is a surprising one—of facts dominated by concepts, of errors repeated and compounded, of evidence dismissed and forgotten, all in the service of vague doctrines of questionable origin and even more questionable value that were never established.

Verrey assumed, reasonably in the context of the time, that the colour centre in the fusiform and lingual gyri was part of the primary visual receptive area. In the ensuing battle to determine the precise limits of the latter area, his evidence and that of others was lost, the primary visual cortex became the visual perceptive centre and was thought to be the sole centre mediating colour vision, along with other attributes of the visual scene. Overcoming this notion has meant modifying concepts of the association cortex, of vision as a process and of the role of the cerebral cortex in it. This was achieved through the experimental demonstration of functional specialization and of separate cortical areas dealing with colour, form and motion in the prestriate visual cortex, as well as the demonstration of specialized colour subregions in V1 and V2 which connect selectively with area V4.

The last part of this review shows how much more we have yet to learn about the visual cortex in general and about the syndrome of achromatopsia in particular. But, in a sense, the demonstration of the colour pathways in the normal human subject with PET brings a chapter in the history of colour vision to a close. That chapter was started by Verrey in 1888. His concluding remarks serve as well to conclude this article. 'Tout ceci nous montre combien de questions sont encore à résoudre dans ce domaine des localisations cérébrales et combien nous nous mouvons encore sur un terrain peu ferme. Cependant toute nouvelle contribution à cette étude a son importance pour l'édification de ce monument dont Charcot et ses élèves ont été les fondateurs, et c'est là ce qui m'a engagé à publier l'observation précédente.'

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APPENDIX

1. Alexander (1881) is referred to, but mistakenly, by Wilbrand and Saenger (1904) in whose bibliography the paper is given as published in the *Archiv für Ophthalmologie* of 1881. The mistake is repeated in the article by Mills (1906), who must have copied it without checking it. In fact, no paper with such an author appears in the relevant journal and I have not been able to trace it.

2. For the sake of clarity, I have slightly altered Henschen's statement here. Henschen was in fact writing about Hitzig's contention that visual impressions are 'received' by the lateral geniculate nucleus and said, 'In other words, one saw with the corpus geniculate externum and understood with the visual cortex' (Henschen, 1930).

3. Wilbrand and Saenger, in *Neurologie des Auges* (1904), and Steffan (1881) do make allusions to colour theory in the classical sense. Helmholtz comes out well in these brief discussions, Hering rather less so.

MUSCLE FATIGUE IN McARDLE'S DISEASE

MUSCLE FIBRE CONDUCTION VELOCITY AND SURFACE EMG FREQUENCY SPECTRUM DURING ISCHAEMIC EXERCISE

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SUMMARY

The origin of fatigue in McArdle's disease is still a matter of debate. Both a reduction of muscle membrane excitability and failure of excitation-contraction (E-C) coupling have been suggested as causes. We performed intermittent isometric biceps brachii contractions (80% maximal voluntary contraction, rate 30/min) under local ischaemia in 5 McArdle's disease patients and 26 healthy controls. Our results show that in McArdle's disease the exerted force is less, the surface EMG (SEMG) amplitude steadily increases, and that the power density spectrum (PDS) shifts to lower frequencies, the latter without significant differences when compared with normals. The most important finding is that muscle membrane excitability remains unimpaired during ischaemic exercise, establishing a dominant role for intramuscular lactic acid formation in the reduction of muscle fibre conduction velocity seen in normal subjects. As is indicated by the shift of the PDS towards lower frequencies, as well as by the increase in SEMG amplitude, it can be concluded that during ischaemic exercise in patients with myophosphorylase deficiency, fatigue occurs without alterations in muscle membrane excitability and is due to a failure of E-C coupling.

INTRODUCTION

Patients with McArdle's disease rapidly fatigue during exercise. After some minutes of exercise they pass through an adaptation phase with exertional myalgia and fatigue, when muscle metabolism is largely dependent on glycogenolysis. Following this phase they become capable of performing at identical force levels and endurance times as normal subjects because of unimpaired fatty acid oxidation (Braakhekke *et al.*, 1986). The precise mechanism of fatigue in patients with myophosphorylase deficiency is a matter of discussion.

Surface electromyography (SEMG) has become an important tool in the investigation of muscle fatigue. Mills and Edwards (1984) showed that during sustained maximal quadriceps contractions, a significantly more pronounced decline of force and a steeper shift of the power density spectrum (PDS) of the SEMG to lower frequencies occurs in McArdle's disease patients as compared with normals. Intramuscular lactate accumulation thus appears not to be obligatory in causing the spectral shift. They postulated that the changes in the PDS are caused by a disturbance in muscle membrane excitability, probably due to an extracellular increase of potassium ions. During exercise at a low force level, Braakhekke *et al.* (1986) showed that the SEMG amplitude showed

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a substantial increase indicating a fatiguing contractile mechanism during the adaptation phase in myophosphorylase deficiency. The PDS, however, did not show consistent changes during this phase. These authors stated that fatigue in McArdle's disease is due to a failure in the muscle excitation-contraction (E-C) coupling. From muscle stimulation studies after ulnar nerve stimulation at the wrist, Wiles *et al.* (1981) concluded that the ultimate cause of force fatigue in the adductor pollicis muscle in McArdle's disease is failure of excitation either at the neuromuscular junction or in the sarcolemma, because the reduction in force was found to be associated with a similar reduction in the compound muscle action potential amplitude. Recently Cooper *et al.* (1989) showed that after high frequency stimulation of the ulnar nerve, the excessive reduction of force in adductor pollicis in McArdle's disease patients was not associated with an excessive decline in excitation, studied as compound muscle action potential amplitude. It is concluded that myofibrillar activation failure occurs over and above that caused solely by excitation failure.

In studying muscle fatigue, usually two electromyographic parameters are analysed: changes in the frequency content by analysis of the PDS and changes of the SEMG amplitude. A less frequently analysed, but well accepted, additional parameter is muscle fibre conduction velocity (MFCV). A changing MFCV is the most direct electroneurophysiological sign of a changing excitability of the muscle fibre membrane. It is generally found that the mean or median frequency of PDS shifts to lower values during fatiguing exercise (e.g., Bigland-Ritchie and Woods, 1984; De Luca, 1984; Mills and Edwards, 1984; Arendt-Nielsen and Mills, 1985; Moritani *et al.*, 1986; Arendt-Nielsen *et al.*, 1989). One of the major factors held responsible for this shift is a decline of MFCV (e.g., De Luca, 1984; Moritani *et al.*, 1984; Arendt-Nielsen and Mills, 1985; Eberstein and Beattie, 1985; Zwarts *et al.*, 1987; Juel, 1988; Arendt-Nielsen *et al.*, 1989). The slowing of MFCV is thought to be due to the intramuscular accumulation of lactic acid (Mortimer *et al.*, 1970; De Luca, 1984; Merletti *et al.*, 1984; Moritani *et al.*, 1984). The mean frequency was found to decrease linearly with lactate accumulation (Tesch *et al.*, 1983; Moritani *et al.*, 1984).

A common finding is an increase in SEMG amplitude during submaximal exercise at a constant force level with prolonged duration (Moritani *et al.*, 1986; Christensen and Fuglsang-Frederiksen, 1988; Arendt-Nielsen *et al.*, 1989). Several factors are held responsible for this increase. The three most important factors are (1) recruitment of additional motor units (Häkkinen and Komi, 1983; Bigland-Ritchie and Woods, 1984; De Luca, 1984; Moritani *et al.*, 1984); (2) changes in the firing frequency characteristics of individual motor units (Häkkinen and Komi, 1983; Bigland-Ritchie and Woods, 1984) compensating for the declining force generating capacity of the individual motor units; and (3) synchronization of motor unit firing patterns (Bigland-Ritchie *et al.*, 1983; De Luca, 1984; Broman *et al.*, 1985; Kuorinka, 1988), and also changes in MFCV and/or the EMG power density spectrum (Lindström and Petersén, 1983; Bigland-Ritchie and Woods, 1984; De Luca, 1984; Arendt-Nielsen *et al.*, 1989).

The present study describes the analysis of the MFCV together with the PDS and the SEMG amplitude in myophosphorylase deficient patients by performing intermittent ischaemic biceps brachii contractions at 80% maximal voluntary contraction.

MATERIAL AND METHODS

Five patients with McArdle's disease and 26 healthy controls volunteered in our experimental protocol. All gave their informed consent. The Committee on Experiments in Humans of the Faculty of Medicine approved the experimental protocol. All 26 controls were right-handed, in good health and without neuromuscular complaints. Their mean age was 36.0 yrs.

The 5 patients with myophosphorylase deficiency were diagnosed on the basis of their complaints about (1) muscle fatigue, (2) exertional myalgia, (3) second wind phenomenon, (4) results of standardized ischaemic forearm exercise tests (Sinkeler *et al.*, 1986), which shows no increase of lactic acid in venous return blood, and (5) absence of myophosphorylase in a histochemical and biochemical biopsy specimen of the quadriceps muscle. In these specimens no evidence of muscle fibre loss was found. There were 2 male and 3 female patients. The mean age was 31.4 yrs. A biopsy was not performed in 1 patient; she was the younger sister of one of the female patients. She had muscle symptoms, an elevated serum creatine kinase level and no increase in lactate during ischaemic exercise, all being compatible with the diagnosis. In 3 patients SDS-electrophoresis was performed which showed absent myophosphorylase enzyme protein. These data are summarized in Table 1.

The fat distribution index (i.e., percentage of body weight (FDI); Durnin and Womeraley, 1974) was determined in most subjects since EMG parameters depend on the subcutaneous fat content (Lindström and Petersén, 1983; Stegeman *et al.*, 1989).

TABLE 1 McARDLE'S DISEASE PATIENTS

Sex	Age (yrs)	Comp ¹	SecW ²	%LacR ³	PT ⁴ (s)	FDI ⁵ (%)	Fibre type ⁶	Force (N)
M	65	+	+	34	30	35.8	35%	133.9
M	26	+	+	52	24	19.7	32%	151.9
F	29	+	+	50	32	40.0	56%	64.0
F	24	+	+	25	57	37.0	57%	60.9
F	13	+	+	12	60	33.0	n.d.	29.7

¹ Complaints about muscle fatigue and exertional myalgia, ² second wind phenomenon, ³ percentage maximal lactate rise in standardized ischaemic forearm test (normal >300%); ⁴ performance time; ⁵ fat distribution index, ⁶ fibre type distribution in percentage of type I fibres (normal 35–50%, 5% confidence level), n.d. = not determined.

Experimental design

Our experimental protocol was designed for the right biceps brachii muscle. Subjects were seated and firmly attached to the biceps dynamometer (Sollie *et al.*, 1985) (fig. 1A). The right arm was fixed in a horizontal position, the elbow being nearly at a right angle. The hand was pronated.

We used a specially designed surface electrode array consisting of 4 gold-coated electrodes placed in line. The electrode diameter was 2 mm and the interelectrode distance 6 mm (fig. 1C). The skin was carefully abraded and cleaned with ethanol. No electrode paste was used in order to avoid low resistance bridges between the closely spaced electrodes.

A small cuff (8 cm) was placed around the upper arm, as far proximally as possible. Much care was taken in positioning the SEMG array parallel to the direction of the muscle fibres of the short head of biceps, distal to the motor point (fig. 1B). Bipolar SEMG signals were derived from electrodes 1 and 2 and electrodes 3 and 4, respectively (fig. 1C). The interrecording distance was therefore 12 mm.

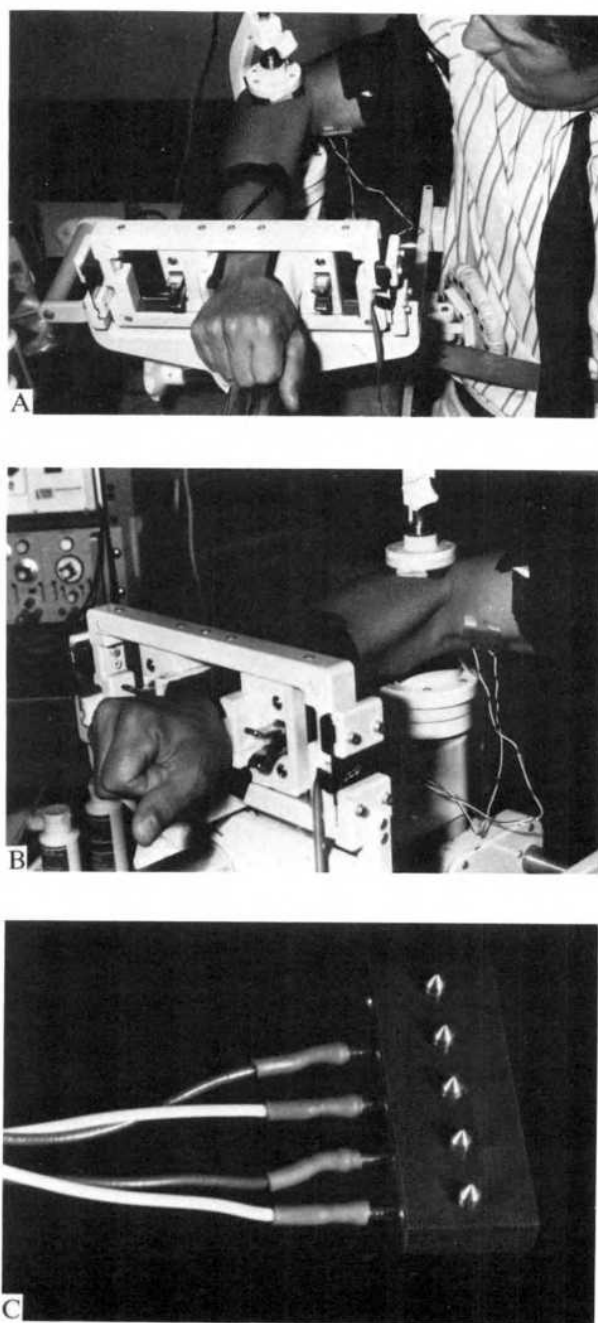


FIG. 1. A, subjects are seated and firmly attached to the biceps dynamometer. B, the right arm is horizontally fixed with the elbow nearly at a right-angle. The surface electrode array is positioned distal to the motor point. C, detail of the surface electrode array.

The SEMG signals were amplified and band pass filtered (5–500 Hz) with amplifiers of our own design, A/D converted (12 bits), sampled (sampling frequency 1700 Hz), and stored on magnetic disc (PDP 11/10 configuration, Digital Equipment Corp.). The exerted force was also digitized and fed into the computer. The analog SEMG signals were visualized on an oscilloscope screen and compared by calculating the cross-correlation function. The electrode array was fixed to the skin when the maximum cross-correlation exceeded 0.7 at a moderate force level.

After electrode positioning, the level of maximal voluntary contraction (MVC) was determined twice with 1 min of rest between. Thereafter all subjects relaxed for 10 min. At 5 s before the start of the experiment the cuff was inflated above 200 mmHg. Intermittent ischaemic contractions of biceps at 80% MVC and a rate of 30/min were then performed until exhaustion. The protocol used intermittent contractions because of the analogy with the standardized ischaemic forearm exercise test, during which significantly more lactic acid is normally formed than during a sustained contraction (Sinkeler *et al.*, 1986).

During the experiment, visual feedback on the performance was achieved on a paper writer. We encouraged the subjects verbally to maintain their force level at 80% MVC for as long as possible. Failure was defined as the moment when they could no longer reach the 80% MVC force level. Performance time was determined from the start of the test until this failure point. After passing the failure point the subjects continued until exhaustion, after which the cuff was deflated.

Performance time in patients with McArdle's disease was limited to 60 s in 4 patients and to 25 s in 1 patient. This limitation of performance time was based on previous experience with the ischaemic forearm exercise test to avoid contractures and/or rhabdomyolysis. During these ischaemic forearm tests all the McArdle's disease patients had passed failure point within the chosen time limits. Twelve volunteers performed the procedure twice to determine reproducibility.

Data analysis

The data were analysed off-line with a PDP 11/34 computer. As a first step, the force peaks with an approximately 2 s periodicity were identified. The almost coincidental EMG bursts were localized. This localization was done by determining local maxima after rectification and rectangular windowing of the EMG over 0.5 s. Following these preprocessing steps, the frequency spectra of the subsequent EMG bursts in both channels were calculated by using the fast fourier transform algorithm. Five parameters were derived. From the frequency spectrum 3 percentiles of the PDS distribution were determined: (1) the 10th (P10), (2) the 50th (= median frequency (F_{med})) and (3) the 90th (P90) percentiles. (4) The root mean square (RMS) value of the burst centre was used as a measure of SEMG amplitude; and (5) the MFCV was determined by combining the frequency spectra of channels 1 and 2 to obtain the phase difference between the two channels for each frequency component separately. Under the assumption of a constant time delay between the two channels, this phase shift should be proportional to frequency. The proportionality factor can be determined by a linear regression on the phase difference versus frequency relation. The phase difference at a specific frequency was weighted in this regression by the amplitude of the PDS at that frequency in both spectra. This method is analogous to the method evaluated by van der Vliet *et al.* (1980). It allows for an accurate determination of the time delay between the two channels as checked by simulation studies (D. F. Stegeman, 1989, unpublished). The MFCV was determined combining this delay with the interchannel distance (12 mm). The change of the 5 parameters as a function of time or burst sequence was the basic measurement performed in order to study the electrophysiological effects of fatigue. Data analysis was undertaken over the performance time period.

The change of most parameters as a function of time during the test was expressed by the two linear regression parameters (intercept, slope). In order to account for the SEMG amplitude in relation to the exerted force a parameter was defined as the normalized amplitude. By dividing the SEMG RMS-amplitude and force (ampl/F ($\mu\text{V}/\text{N}$)) an attempt was made to study the efficiency between the central drive and force generation (neuromuscular efficiency). Guided by the character of the results, this SEMG amplitude function was characterized by a nonlinear quadratic regression (fig. 2). The resulting parabolic fit through the data was expressed in 5 values at 0%, 25%, 50%, 75% and 100% of the performance time period (fig. 5).

Spearman correlations and Student's *t* test were used for statistical evaluations. Differences from normals are expressed at *P* values unless otherwise stated. Results are given as means $\pm$ SD.

RESULTS

During the intermittent ischaemic biceps contractions at 80% MVC, a continuous almost linear decline of Fmed, P10, P90, and MFCV was found in healthy volunteers.

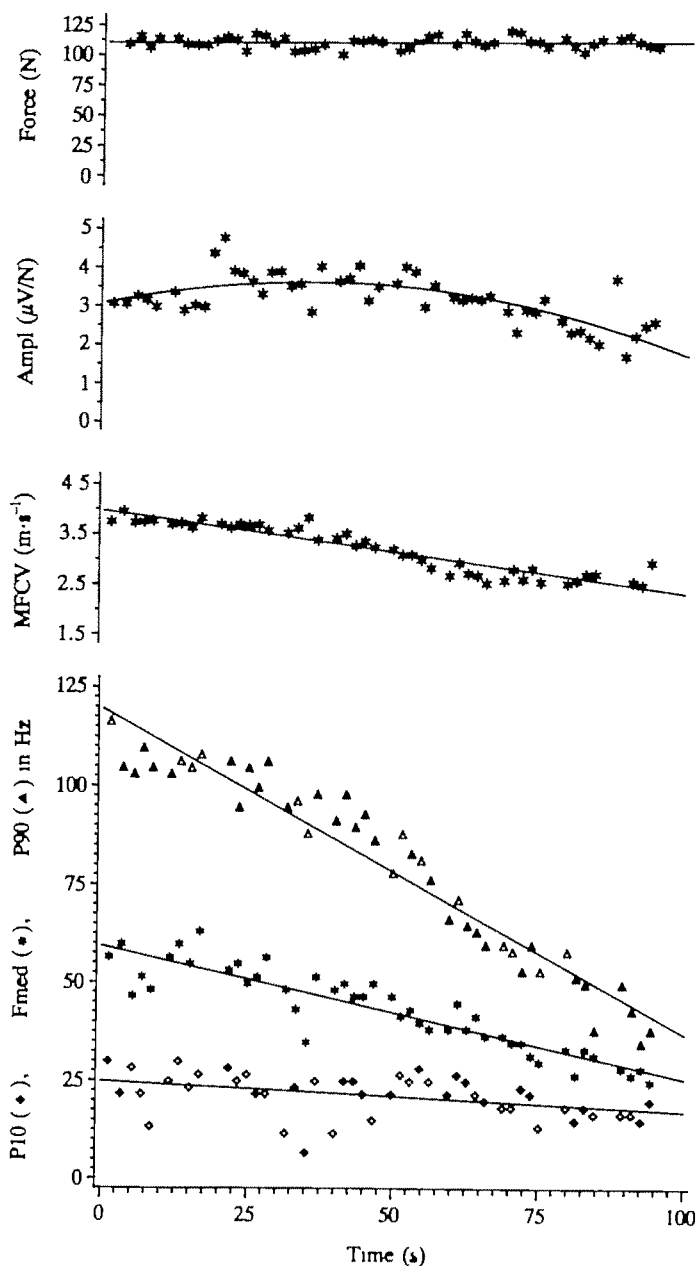


FIG. 2. Example of the changes occurring in 4 parameters during a surface electromyographic (SEMG) recording over 95 s in a healthy volunteer, showing force, amplitude of SEMG, muscle fibre conduction velocity, and 3 percentiles of the power density spectrum (P10, P50 (Fmed), P90).

Initially the SEMG amplitude showed a slight increase, then at halfway reached a maximum after which the amplitude declined again. An example is given in fig. 2.

The data are summarized in Table 2 and fig. 3. Only the most prominent findings are presented in detail here. In Table 2 the data of the individual McArdle's disease patients and the mean values of the SEMG parameters of controls are given.

TABLE 2 SEMG DATA

	<i>McArdle's disease</i>			<i>Controls</i>		
	<i>Male</i> ¹ (<i>n</i> =2)	<i>Female</i> ¹ (<i>n</i> =3)	<i>Total</i> (<i>n</i> =5)	<i>Male</i> (<i>n</i> =12)	<i>Female</i> (<i>n</i> =14)	<i>Total</i> (<i>n</i> =26)
Mean force (N)	133.9** 151.9	64.0** 60.9 29.7	88.1* ±52.2	199.5** ±45.9	115.1** ±30.0	154.1* ±56.8
Slope Ampl/F 0-25% ²	0.047** 0.096	0.018** 0.027 0.033	0.044** ±0.031	0.040** ±0.048	0.024** ±0.023	0.032** ±0.037
Slope Ampl/F 75-100% ³	0.018** -0.010	0.114*** 0.068 0.100	0.058* ±0.053	0.008** ±0.032	-0.026*** ±0.038	-0.018* ±0.036
Initial Fmed ⁴ (Hz)	135.3** 99.9	56.7* 55.9 78.2	85.2** ±33.3	124.7** ±33.4	98.4* ±32.6	110.6** ±35.0
Slope Fmed (Hz·s ⁻¹)	-0.04** -1.37	-0.21*** -0.04 -0.22	-0.37** ±0.57	-1.05** ±0.55	-0.64*** ±0.37	-0.83** ±0.50
Initial MFCV ⁵ (m·s ⁻¹)	4.42** 4.62	3.99*** 4.01 4.14	4.24** ±0.28	5.03** ±0.85	4.68*** ±0.67	4.84** ±0.76
Slope MFCV (m·s ⁻²)	0.0032*** -0.0041	-0.0005**** -0.0029 -0.0021	-0.0013**** ±0.003	-0.029*** ±0.018	-0.025**** ±0.015	-0.027**** ±0.016

¹ In McArdle's disease patients, individual data are presented. ² Slope of SEMG amplitude increase from 0-25%, and ³ from 75-100% of the performance time, ⁴ initial value and slope of the median frequency of the power density spectrum, ⁵ initial value and slope of muscle fibre conduction velocity. All comparisons are made between McArdle's disease patients and controls. Males are compared with males, females with females and total with total. * = $P < 0.05$, ** = $P < 0.01$; *** = $P < 0.005$, **** = $P < 0.001$ n.s. = not significant.

In McArdle's disease the mean exerted force (88.1 N) was significantly lower compared with controls (154.1 N, $P < 0.05$). In the 2 male McArdle's disease patients the initial force levels were within the normal range (152 N and 134 N). These male patients had more type 2 fibres in their muscle biopsy specimen (Table 1). They exerted higher forces than the 2 female patients (64 N, 61 N) with a type 1 fibre predominance (> 55% type 1 fibres (Dubowitz and Brooke, 1973)).

The mean performance time was less in McArdle's disease (40.6 ± 14.5 s) as compared with controls (72.0 ± 17.9 s, $P < 0.01$). Especially in those patients with a higher

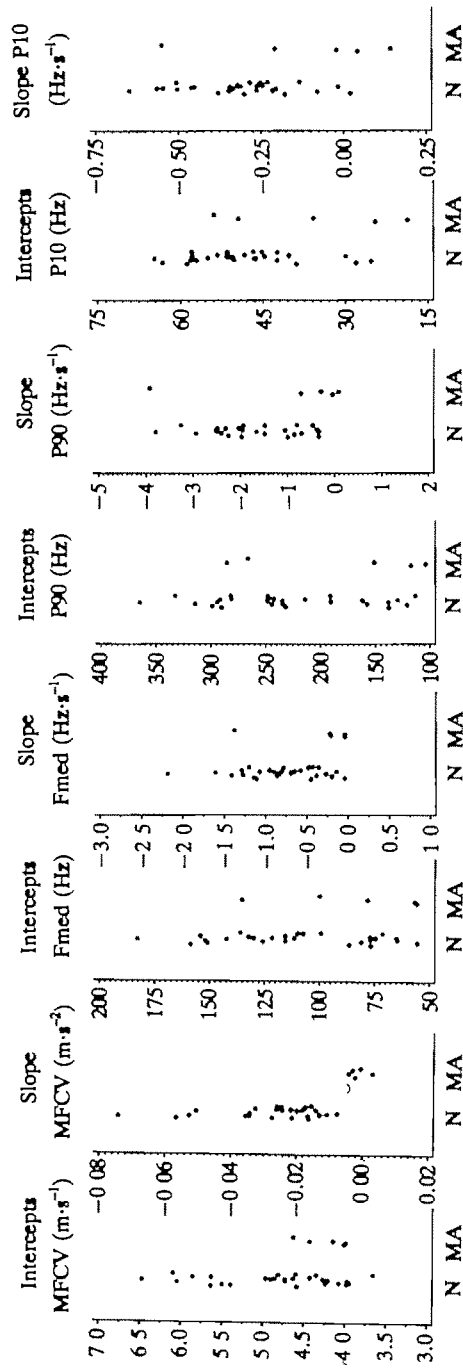


Fig. 3. Scatter diagrams for the intercepts (initial values) and slopes of the muscle fibre conduction velocity (MFCV), the median frequency (Fmed) as well as the 90th and 10th percentiles (P90, P10) of the power density spectrum. Normals (N) are compared with McArdle's disease patients (MA). See also Table 2. * = male, ◊ = female.

percentage of type 2 fibres, the performance time (24 s and 30 s, Table 1) was shortened. Analysis of the SEMG results of controls only over the mean performance time period of the McArdle's disease patients revealed the same conclusions, which indicated that our findings were not determined by the marked differences in performance time between McArdle's disease and control subjects.

In McArdle's disease the mean MFCV was initially lower ($4.24 \text{ m}\cdot\text{s}^{-1}$) compared with controls ($4.84 \text{ m}\cdot\text{s}^{-1}$, $P < 0.01$). The MFCV, however, showed little change (mean slope: $-0.0013 \text{ m}\cdot\text{s}^{-2}$) during anaerobic exercise in the McArdle's disease patients, which is significantly different from the MFCV decline in controls ($-0.027 \text{ m}\cdot\text{s}^{-2}$, $P < 0.001$, Table 2, figs 3, 4).

The PDS showed a shift of Fmed, P10 and P90 to lower frequencies in controls. The mean initial and mean slope values for these frequency parameters are summarized in Table 2 and fig. 3. In McArdle's disease patients the mean initial median frequency (85.2 Hz) of the PDS distribution did not differ significantly compared with controls (110.6 Hz). The mean slope of Fmed decrease was $-0.37 \text{ Hz}\cdot\text{s}^{-1}$, which was also not significantly different when the McArdle's disease patients were compared with controls ($-0.83 \text{ Hz}\cdot\text{s}^{-1}$).

In myophosphorylase deficiency the changes in the P90 and P10 percentiles of the PDS distribution showed no notable differences when compared with normals. Roughly speaking, the relative decline of the P90 (as a percentage of the intercept) was equal to the decline in relative Fmed, both in patients and in controls. The P10 showed relatively less decline in both groups (figs 2, 3).

In the myophosphorylase deficient patients the normalized SEMG amplitude (Ampl/F ($\mu\text{V}/\text{N}$)) showed a steady increase during the experiment. Initially the normalized SEMG amplitude in all McArdle's disease patients was low ($2.96 \pm 0.5 \mu\text{V}/\text{N}$) compared with normals ($3.38 \pm 1.93 \mu\text{V}/\text{N}$). The amplitude then steadily increased until a maximum was reached at the failure point, which was higher than the maximum in normals (fig. 5). This behaviour was dominated by the increase of SEMG amplitude in female patients. The mean slope of amplitude increase in McArdle's disease patients ($0.044 \mu\text{V}/\text{N}\cdot\text{s}^{-1}$) showed no significant difference from controls ($0.032 \mu\text{V}/\text{N}\cdot\text{s}^{-1}$) from the start to 25% of performance time (Table 2). From 75% to 100% of performance time, however, the SEMG amplitude increased in McArdle's disease patients ($0.058 \mu\text{V}/\text{N}\cdot\text{s}^{-1}$), while in normals the mean amplitude declined (slope: $-0.018 \mu\text{V}/\text{N}\cdot\text{s}^{-1}$, $P < 0.05$).

It appeared that female McArdle's disease patients differed significantly from their male counterparts with respect to most parameters (figs 3, 5, Table 2), except for the absence of a decline in MFCV. The mean fat distribution index (FDI) in McArdle's disease patients ($33.1\% \pm 7.9\%$) was not significantly different when compared with controls ($24.4\% \pm 5.7\%$).

DISCUSSION

Muscle fibre conduction velocity

The present study clearly shows that MFCV does not decline during intermittent ischaemic biceps brachii contractions at 80% MVC in patients with McArdle's disease (fig. 4). MFCV is a sensitive neurophysiological indicator of muscle membrane integrity.

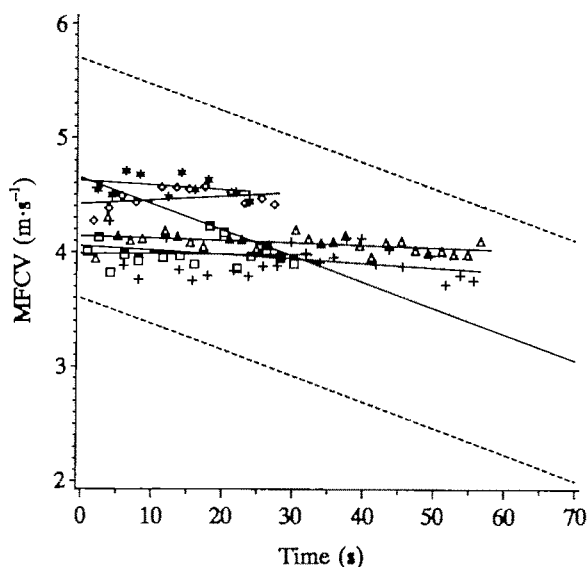


FIG. 4. Muscle fibre conduction velocity (MFCV) in 5 patients with McArdle's disease (*, +, □, △, ◇) during intermittent ischaemic exercise. For controls, the linear regression analysis is performed on pooled MFCV data, 90% confidence limits are included (dotted lines). For McArdle's disease patients, individual linear regression lines are presented. This presentation is intended for illustrative and not for comparative statistics.

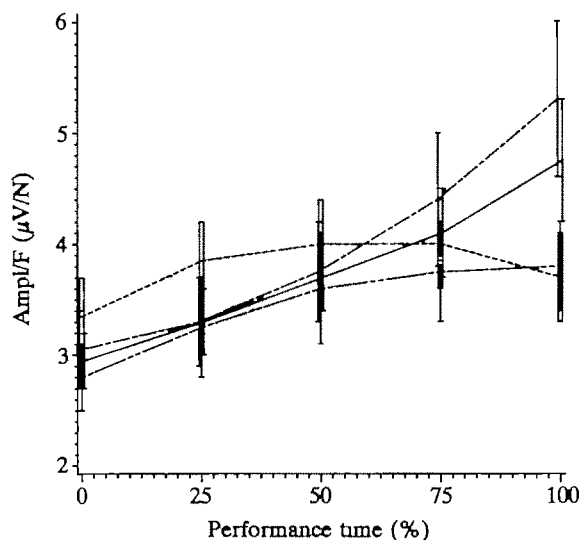


FIG. 5. Relationship between amplitude $\pm$ SD for surface electromyographic recordings (Ampl/F (μ V/N)) and performance time. Normals (---), McArdle's disease (—), male (—○—) and female (—□—) McArdle's disease patients.

In normal healthy subjects we found a steady and almost linear decline of MFCV. This finding is of major importance with regard to what can be called the 'lactate hypothesis'. An intramuscular accumulation of lactic acid is generally held to be responsible for

the slowing of MFCV (Mortimer *et al.*, 1970; De Luca, 1984; Merletti *et al.*, 1984; Broman *et al.*, 1985). Lactic acid is formed in the glycogenolytic pathway, mainly by the type 2 fibres at higher force levels (Tesch, 1980; Tesch *et al.*, 1982; Häkkinen and Komi, 1983; Kereshi *et al.*, 1983; De Luca, 1984; Broman *et al.*, 1985; Juel, 1988). Muscle metabolism is functionally ischaemic at higher force levels (Bigland-Ritchie *et al.*, 1981; De Luca, 1984; Zwarts and Arendt-Nielsen, 1988). The accumulation of lactate results in a lowering of intramuscular pH, which apparently causes a decrease of membrane excitability, probably due to the pH dependency of the sodium-potassium pump (Bigland-Ritchie, 1979; Sjøgaard, 1986; Miller *et al.*, 1987; Juel, 1988). Impairment of membrane excitability causes a decline of MFCV (De Luca, 1984; Horita and Ishiko, 1987; Miller *et al.*, 1987).

In patients with myophosphorylase deficiency there is an inability to use muscle glycogen as fuel, which results in no or only minimal lactate formation during ischaemic exercise (Table 1). Intramuscular pH showed no fall when studied by ^{31}P nuclear magnetic resonance (Ross *et al.*, 1981). The absence of any definite decline of MFCV in patients with McArdle's disease strongly supports the statement that lactate is the main cause for MFCV decline. The result suggests an unimpaired muscle membrane excitability in fatigued myophosphorylase deficient patients. This latter finding is important with regard to the general discussion on where muscle fatigue originates in general and in McArdle's disease in particular.

Power density spectrum

Many authors have reported a shift of PDS to lower frequency in muscle fatigue (e.g., Bigland-Ritchie *et al.*, 1981; Häkkinen and Komi, 1983; Kereshi *et al.*, 1983; Naeije and Zorn, 1983; De Luca, 1984; Mills and Edwards, 1984; Eberstein and Beattie, 1985; Kranz *et al.*, 1985; Moritani *et al.*, 1986; Zwarts *et al.*, 1987). Two major mechanisms are thought to cause this shift: a decrease of MFCV and the changing statistics of the motor unit firing patterns, such as synchronization (Bigland-Ritchie *et al.*, 1983; De Luca, 1984; Mills and Edwards, 1984). Other factors determining the PDS distribution are the volume conduction characteristics acting as a low pass filter (Lindström and Petersén, 1983; De Luca, 1984), the exerted force level (Moritani *et al.*, 1986), and muscle temperature (Petrofsky and Lind, 1980).

In the present experiments we found a definite shift of Fmed to lower frequencies both in patients and controls. The decay of the Fmed showed no significant differences compared with normals, although there was a tendency for a less pronounced Fmed decline in McArdle's disease (fig. 3, Table 2). This seems to contradict the findings of Mills and Edwards (1984). During sustained maximal voluntary contractions of the quadriceps muscle they found a decline of force and a fall of mean power frequency (MPF) that was larger in McArdle's disease patients than in normals. Without performing MFCV measurements, Mills and Edwards (1984) suggested that in McArdle's disease excitation-contraction (E-C) coupling remains unimpaired, whereas membrane excitability decreases. They hypothesized that the available energy is preferentially used for cross-bridge cycling at the expense of membrane integrity. As a result, the extracellular potassium ion concentration will increase and may cause the power spectral changes of the SEMG. It is difficult to imagine how such changes take place without affecting the MFCV, which was not measured by these authors. Braakhekke *et al.* (1986) showed

in patients with McArdle's disease that during the adaptation phase the median frequency of PDS showed no consistent changes and in that respect did not differ from normals. Differences in the experimental protocol are apparently very important for the behaviour of the PDS.

Some authors have reported that the percentage fall of MPF always exceeds that of MFCV (Arendt-Nielsen *et al.*, 1984; Broman *et al.*, 1985; Zwarts *et al.*, 1987), whereas others have found a proportional relationship between the decrease in MFCV and Fmed (Lindström and Petersén, 1983; De Luca, 1984; Merletti *et al.*, 1984; Arendt-Nielsen and Mills, 1985; Eberstein and Beattie, 1985). Our findings are in accordance with the first group of authors and again show that MFCV cannot be the only factor determining the shift of PDS.

How can the shift of PDS be explained in the absence of an alteration in MFCV? The factors other than MFCV that influence the PDS have already been mentioned. We did not record the intramuscular temperature, but a reduction in muscle temperature would affect MFCV. However, an increase of intramuscular temperature would have been more likely. The exerted force level was constant and therefore could not explain the shift of PDS during exercise. The thickness of the subcutaneous fat layer, which partly determines the volume conduction characteristics for SEMG recording, was not more pronounced in our patients. The FDI thus cannot account for the differences of PDS behaviour between patients with McArdle's disease and normals. After exclusion of mechanisms capable of influencing the PDS, the most probable explanation for the shift of PDS to lower frequencies seems to be an increase in synchronization between the motor unit firing patterns.

SEMG amplitude

After dividing the SEMG amplitude by the exerted force ($\mu\text{V}/\text{N}$), the normalized amplitude is seen to be within the same range for McArdle's disease patients as well as for controls (fig. 5). This indicates that the contractile properties (neuromuscular efficiency) of the muscle fibres are almost identical in both groups. In normals the SEMG amplitude starts declining halfway through performance time. Since the force level is maintained, it is not likely that a reduction in the number of active motor units and/or changes of the motor unit firing characteristics cause the decline of SEMG amplitude. Simulation studies indicate that one of the consequences of a decline of MFCV is a decrease in SEMG amplitude (Lateva, 1988). Probably the decrease of SEMG amplitude in normals is caused by a decline of MFCV. It can therefore be argued that the explanation of the 60% increment in SEMG amplitude in McArdle's disease is probably related to an increase in motor unit firing frequencies and possibly to increased synchronization between firing patterns. Additional recruitment of motor units seems unlikely at an 80% MVC level (Sale, 1987).

Lateva (1988) reported an almost proportional effect of MFCV alone on surface EMG amplitude. It is possible to use that proportionality to remove the effect of MFCV on amplitude. The average percentage fall of MFCV in normals is 35%. Absence of this decay of MFCV would result in a 65% increase in normal SEMG amplitude, a value close to that found in McArdle's disease patients (59%). This indicates that the process that counteracts the decrease in neuromuscular efficiency during fatiguing exercise is

similar in patients with McArdle's disease and in normals, not to mention the differences in performance time.

Another finding is that female McArdle's disease patients differ significantly from male patients for all parameters except for the absence of a decrease in MFCV. It can be hypothesized that this finding is related to the type 1 fibre predominance in the female since the low force-generating capacity (Broman *et al.*, 1986; Ruff, 1989), the low initial MFCV (Broman *et al.*, 1985; Arendt-Nielsen *et al.*, 1989) and the low initial power density frequency content (Milner-Brown *et al.*, 1986) all point to a predominant type 1 fibre utilization. The short performance time in the male McArdle's disease patients points to the rapid fatiguability of type 2 muscle fibres. In fact, during ischaemic exercise, type 2 muscle fibres are of little benefit in McArdle's disease because of their mainly glycogenolytic metabolism.

The absence of a decrease in MFCV, indicating intact action potential transmission, the normal changes in PDS and the almost identical neuromuscular efficiency lead to the conclusion that fatigue in McArdle's disease is not due to a loss of excitability of the muscle fibre membrane. This conclusion is consistent with the findings of Cooper *et al.* (1989), who found that fatigue in myophosphorylase deficiency after indirect high frequency stimulation is due to failure of excitation-contraction coupling. These authors also found some evidence for additional excitation failure. Perhaps the differences between the experimental protocols, for example, supramaximal muscle stimulation as against submaximal voluntary contraction, account for this finding. In our experiments we certainly found no evidence for excitation failure of the sarcolemma. Excitation failure, if it occurs, can hardly be localized to the sarcolemma in which no signs of dysfunction can be observed. Our experiments support the view that in myophosphorylase deficient patients, as in normals, muscle fatigue is mainly caused by a contractile failure.

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SINGLE UNIT ANALYSIS OF THE HUMAN VENTRAL THALAMIC NUCLEAR GROUP

ACTIVITY CORRELATED WITH MOVEMENT

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SUMMARY

During neurosurgical operations for the relief of movement disorders, single thalamic neurons ($n = 107$) were identified with activity which was related to verbally cued active movements (movement-related cells). The activity of each neuron was examined during different contralateral movements in order to determine the movement which was associated with the most consistent and pronounced change in firing rate (the optimal response). The optimal response was determined by analysis of histograms of neuronal activity which were constructed by using the onset of EMG activity to synchronize successive repetitions of the active movement.

Movement-related cells exhibited optimal responses associated with such movements as making a fist, extension or flexion of the wrist, flexing or extending the elbow, pointing with the entire upper extremity, extending the tongue and lifting the leg. Most movement-related cells recorded in a single parasagittal plane in an individual patient had optimal responses related to movements involving the same part of the body. Movement-related cells were classified into those that were activated in response to somatosensory stimulation (combined cells, $n = 20$) and those which were not (voluntary cells, $n = 87$). Combined cells were activated in advance of EMG activity during active movement and so could be distinguished from cells responding only to sensory stimulation (sensory cells). Movement-related cells (combined and voluntary cell types) were located anterior to sensory cells and tended to show a mediolateral somatotopic organization parallel to that of sensory cells with cutaneous receptive fields. Combined cells responded to somatosensory stimulation of the same part of the body as that involved in the active movement related to the optimal response of the cell. Combined cells responding to passive movements of a joint always had their optimal response during active movement about the same joint. The activity of combined cells during parkinsonian tremor may clarify the role of sensory feedback in tremor.

INTRODUCTION

Microelectrode recordings were first described as a means of localizing targets during stereotactic surgery by Albe-Fessard *et al.* (1962). Since that time, recordings made during surgery have provided examples of human thalamic activity related to active movement (Umbach and Ehrhardt, 1965; Jasper and Bertrand, 1966; Crowell *et al.*, 1968; Siegfried *et al.*, 1969; Bertrand, 1971, 1972; Li and Van Buren, 1972; Raeva, 1972; Umbach, 1972; Hongell *et al.*, 1973; Fukushima and Schramm, 1975; Raeva and Livanov, 1975; Raeva, 1977, 1986). These studies were based on recordings of multiple or single unit activity and analysed either by subjective examination of the records

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(Umbach and Ehrhardt, 1965; Jasper and Bertrand, 1966; Crowell *et al.*, 1968; Siegfried *et al.*, 1969; Bertrand, 1971, 1972; Li and van Buren, 1972; Umbach, 1972; Hongell *et al.*, 1973; Fukushima and Schramm, 1975) or by calculation of instantaneous firing rate during a single movement (Raeva, 1972, 1977, 1986; Raeva and Livanov, 1975). The analysis of histograms constructed from several repetitions of a movement has often been employed in chronic primate studies but has not previously been employed in studies of the human thalamus.

Human thalamic cells responding to passive movement of a joint also show activity related to active movements of the same joint (Jasper and Bertrand, 1966; Raeva, 1986). For these cells, activity related to the active movement is usually a consequence of somatosensory stimulation produced by movement (Jasper and Bertrand, 1966; Raeva, 1986). However, studies in nonhuman primates have shown that some thalamic cells responding to passive movement are activated during active movement by mechanisms which are independent of sensory transmission, that is, combined cells (Strick, 1976b; Horne and Porter, 1980; MacPherson *et al.*, 1980). Current hypotheses about the mechanism of parkinsonian and cerebellar tremor are based on the assumption that combined cells are found in human thalamus and motor cortex (Vilis and Hore, 1980; Stein and Lee, 1981).

We now report results of recordings from human thalamic single neurons with activity related to active movement (movement-related cells). Histograms of neuronal activity were computed by using the onset of EMG activity to synchronize successive repetitions of the movement. The activity of movement-related cells was examined during several different voluntary movements, an experiment readily performed in man because of the unique human ability to respond to a wide range of verbal commands.

A subpopulation of movement-related cells (combined cells) showed activity related to active movement and somatosensory stimulation such that the movement-related activity was not exclusively a response to somatosensory stimulation resulting from movement. Combined cells were defined as cells which were activated both in response to somatosensory stimulation and in advance of EMG onset during active movement. This definition of cell type was used to distinguish combined cells from cells with activity related to active movement alone (voluntary cells), to sensory stimulation alone (sensory cells), or neither to active movement nor sensory stimulation (no-response cells). Based on this classification of cell type, the relative locations and somatotopic organizations of human thalamic cells were determined.

MATERIAL AND METHODS

The population for this study comprised 36 patients with the following conditions: parkinsonian tremor ($n = 11$), cerebellar tremor ($n = 9$), essential tremor ($n = 3$), dystonia ($n = 4$) and chronic pain ($n = 9$). The response to somatosensory stimulation was studied in all patients. Movement-related activity was studied in a subpopulation comprised of 12 patients with the following conditions: parkinsonian tremor ($n = 7$), cerebellar tremor ($n = 3$), essential tremor ($n = 1$) and dystonia ($n = 1$). The protocol used in these studies followed the principles of the Declaration of Helsinki for research involving human beings and was reviewed and approved by the Institutional Review Boards at The Johns Hopkins University and the University of Toronto.

Operating and recording techniques

Thalamotomy was performed as a two-stage procedure employing the Leksell frame (Lenz *et al.*, 1988a).

First, the three dimensional frame coordinates of the anterior and posterior commissures were measured with positive contrast ventriculography or CT scanning. A computer program then reduced or expanded the sagittal sections of the Schaltenbrand and Bailey Atlas (1959) to produce a set of maps conforming to the patients' intercommissural distance (Hawrylyshyn *et al.*, 1976). During the second stage, physiological corroboration of the stereotactic target was performed under local anaesthetic using single unit recording with a high impedance microelectrode (Lenz *et al.*, 1988a).

The platinum-iridium microelectrode used was electrolytically etched to a tip of 3–4 μm and coated with solder glass to give an impedance of approximately 2–4 $\text{m}\Omega$ at 1000 Hz. The distal 1 cm of this electrode was then sheared off and inserted into the end of a 26 gauge insulated stainless steel tube. The microelectrode was fixed to modified hydraulic microdrive (David Kopf Instruments, Tujunga, California, USA) which incorporated a high impedance preamplifier. At operation, a thin-walled stainless steel guide tube with rigid obturator was introduced stereotactically to a point just anterior and dorsal to the ventral thalamic nuclear group. The obturator was then replaced with the microelectrode-preamplifier assembly and the microelectrode progressively advanced using the hydraulic microdrive. The microelectrode signal was recorded and filtered using standard techniques (–6 dB at 300 and 10 000 Hz).

Microelectrode trajectories targeted the ventrocaudal (Vc), ventralis intermedius (Vim) and ventralis oralis posterior (Vop) nuclei of the thalamus in the 14–15 mm lateral plane as located on the computer generated map described above. If cells responding to somatosensory stimulation (sensory cells) or cells firing at approximately tremor frequency ('tremor cells') were not located along these trajectories then additional trajectories were made lateral and/or medial to the plane of the initial trajectory until sensory cells or 'tremor cells' were found. Electrode trajectories were made in virtually parasagittal planes approaching the intercommissural line at angles of 30–70° from above and in front because the access burr hole was always made 15 mm lateral to the midline near the coronal suture, ipsilateral to the target.

As a physiological measure of active movement, electromyograms (EMG) were recorded contralateral to the side of the thalamic recording in up to 8 of the following muscles: masseter, myohyoid, anterior head of deltoid, biceps, flexor and extensor carpi ulnaris, flexor digitorum superficialis and extensor digitorum communis, hypothenars, quadriceps and gastrocnemius. EMG activity was recorded through pairs of silver disc electrodes separated by 5–10 cm and arranged parallel to fibres in the underlying muscle. Electrode positions were checked by asking the patient to perform movements involving primarily one muscle or group of muscles. The EMG signals were amplified, filtered (–6 dB at 6 and 1000 Hz) and continuously monitored on an oscilloscope and an 8 channel polygraph (Model 9, Grass Equipment Corp., Quincy, MA, USA) which had a switching panel allowing selection of 5 EMG channels for storage on a tape recorder (FM bandpass 0–5000 Hz). Action potentials recorded by the microelectrode were discriminated in the operating room and either the microelectrode or discriminator output was fed into an audio monitor.

The microelectrode and EMG signals from 5 muscles were recorded on tape (Model D, Vetter Co., Rebersburg, PE, USA). Finally, the recording included a voice channel to document instructions being given to the patient and descriptions of the site, nature and timing of somatosensory stimulation.

Instruction to patients

As part of their preoperative preparation, patients were trained to make rapid movements in response to verbal commands, as described below. During the operation, when a single unit had been isolated, the patient performed 3 or 4 repetitions of a particular movement, each repetition in response to a rapidly delivered, single word command such as 'squeeze' for making a fist. This technique was used to study the effects of several different movements including: extending the tongue, making a fist, extending or flexing the wrist, flexing or extending the elbow, pointing to a target above the operating table, lifting the leg and dorsiflexing or plantarflexing the foot. Visual and auditory inspection of the response identified the active movement which evoked the most consistent and pronounced change in neuronal firing pattern, termed the optimal response. Finally, a somatosensory examination was carried out to determine whether somatosensory stimulation resulting from movement contributed to movement related activity (Lenz *et al.*, 1988b).

Somatosensory examination

Cells were classified by their activity during active movement and by their response to somatosensory stimulation. Combined and sensory cells were classified as responding to either cutaneous or deep stimuli and as exhibiting either a lemniscal or nonlemniscal response pattern (Poggio and Mountcastle, 1963;

Mountcastle, 1980). Cells (combined and sensory) were classified as responding to deep stimulation if they responded to manipulation of muscles, joints or tendons but not to manipulation of overlying cutaneous structures. A lemniscal response pattern was characterized by a well-defined receptor field, a preferential response to one modality of stimulation and a reproducible response to repeated stimulation. A nonlemniscal response was characterized by a receptive field with a poorly defined boundary, an uncertain optimal modality of stimulation and a variable response to repetitive stimulation. Cells exhibiting a lemniscal response pattern were further classified as rapidly adapting (RA) or slowly adapting (SA) by subjective evaluation of their response to a manual stimulus of approximately 1 s duration.

The operative setting significantly constrained our ability to classify neuronal responses to somatosensory stimulation. It was often difficult to classify cells as responding either to deep or cutaneous stimulation, particularly in the case of units with receptive fields on the hand. Many cells could not be unambiguously classified as RA or SA by their response to manual application of a 1 s stimulus (*see* Table 3). Finally, physiological tremor in the examiner's hand could cause some RA cells to be misclassified as SA.

Data acquisition and analysis

Postoperatively, action potentials from single units recorded on tape were discriminated by size and verified as arising from a single unit by the criterion of constant shape of action potential displayed on a storage oscilloscope. The EMG signal was amplified, full-wave rectified, and low pass filtered (-6 dB at 50 Hz) to produce a signal termed the demodulated EMG. Neuronal and EMG activity were photographed from the oscilloscope screen and digitized for further analysis. Times of occurrence of action potentials were recorded at a clock rate of 1000 Hz while the demodulated EMG signals were digitized at 200 Hz on a CAMAC interface. For 4 patients, the voice channel was rectified, filtered and digitized to indicate the time of occurrence of the verbal cue to move. EMG triggered histograms of thalamic cell activity were calculated on a microcomputer (Hewlett-Packard 9000).

Fig. 1 shows the activity of a neuron which altered its firing pattern in relation to active movement. The heavy line under the microelectrode signal in fig. 1A indicates the verbal instruction to make a fist. Specifically, this line corresponds to the interval over which the rectified, filtered audio signal of the voice exceeded the baseline mean $+3$ SDs level. The demodulated EMG signal is displayed below the microelectrode signal. The onset of EMG activity during active movement was used to establish time 0 for the raster and histogram.

The EMG triggered raster and histogram are shown in panel B. The number of lines in any raster indicates the number of repetitions of that particular movement of that particular cell. Zero time for the histogram was defined as the time at which the demodulated EMG signal in any channel exceeded the baseline mean plus 3 SDs level. The stack of lines above the histogram indicate the timing of the verbal command for corresponding events in the raster. Note that the onset of each verbal command occurred in the interval between the baseline period, consisting of the first 8 bins, and the onset of EMG activity (time 0). The onset of the verbal command occurred in this interval for each of the 32 cells (4 patients) for which the verbal command signal was digitized (*see also* fig. 2B, o).

Subjective criteria were used to identify movement-related cells. Histograms and rasters were considered to exhibit activity related to movement if (1) a minimum of 5 contiguous 50 ms bins had firing rates which were all greater or all less than the mean baseline level, and (2) the change in firing rate occurred over approximately this interval in the majority of events in the raster. The interval of altered firing continued for as long as criteria 1 and 2 were both met. These two criteria were used to select intervals showing a consistent change in cellular activity.

The histogram illustrated in fig. 1B shows an increase and subsequent decrease in the firing rate indicated, respectively, by the solid and dashed lines above the histogram. Similar criteria were used to identify decreases in firing rate, although 1 bin of the series was allowed to exceed the mean baseline level (*see* criterion 1) if criterion 2 was satisfied. Thus fig. 1 illustrates the activity of a cell in the human ventral thalamic nuclear group which changed its firing rate during verbally cued movement and so was termed a 'movement-related cell'.

RESULTS

The present results were based upon studies of 1012 cells. Of these, 521 cells were classified as sensory cells and were located along 56 trajectories in 32 patients

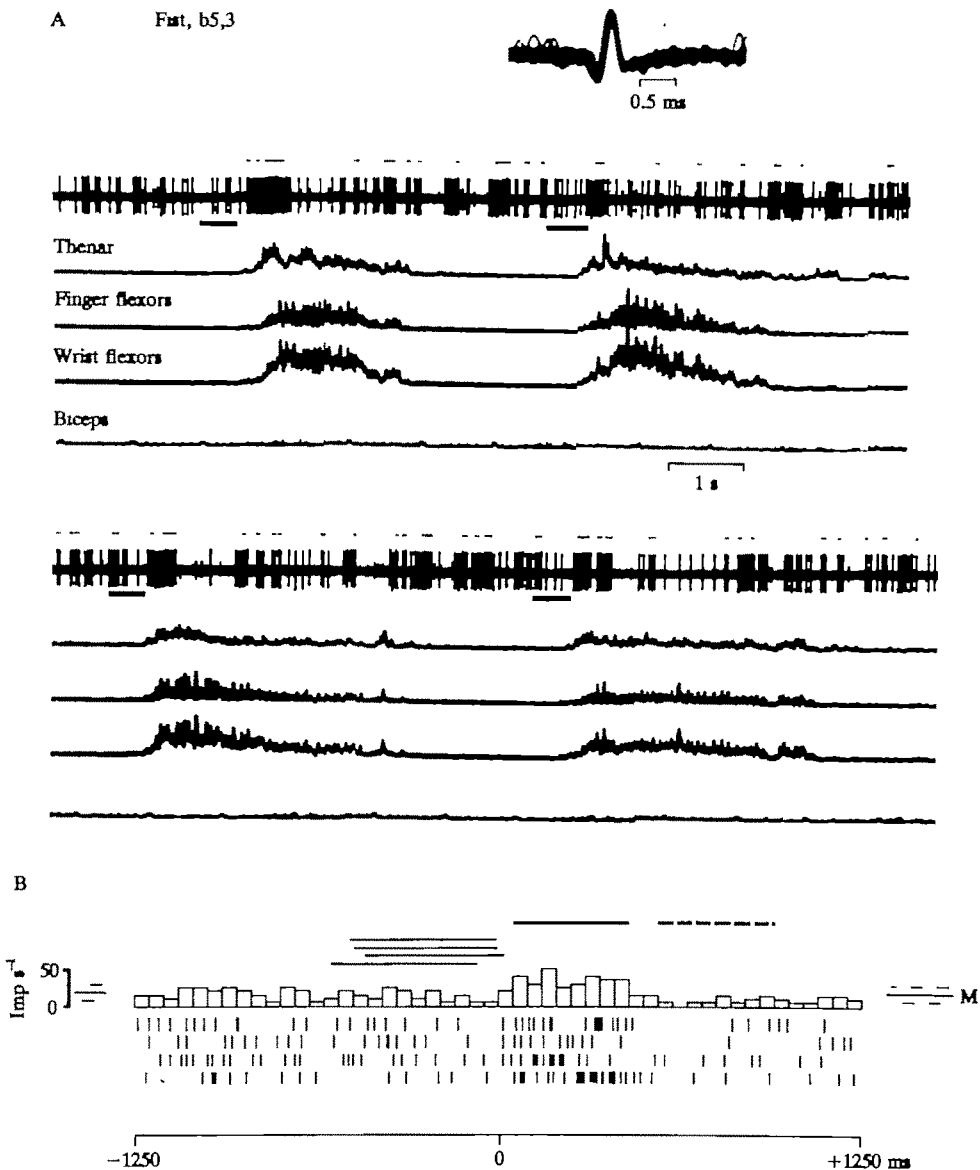


FIG. 1. The activity of a single thalamic neuron and contralateral forearm muscles during the active movement of making a fist. A shows the microelectrode signal in the *upper trace* with the EMG signals of 4 contralateral muscles in the 4 *lower traces*, as labelled. Dots above the microelectrode signal indicate the occurrence of the discriminated action potential whose constant shape is illustrated by the high speed oscilloscope trace in the inset. The *lower panel* is the continuation of the *upper panel*. Each repetition of the movement, indicated by the contralateral forearm EMG signal, has been made in response to the verbal command indicated by the heavy line beneath the microelectrode signal. B shows the raster and histogram of the neuronal activity illustrated in A. Events in the raster are time-locked to the onset of EMG activity as defined in the text. The stack of horizontal lines above the histogram indicates the timing of the verbal command to move for each event in the raster. The mean baseline level for the histogram is indicated by the solid lines, labelled M, to the side of the histogram. Dashed lines above and below these solid lines indicate, respectively, the mean ± 2 SD. The movement performed (fist), patient (b5) and neuron (3) identification numbers are indicated in the upper left-hand corner of A. Calibration bars are as labelled.

(Lenz *et al.*, 1988b); 107 cells were classified as movement-related cells and were located along 21 trajectories in 12 patients; and 20 movement-related cells had properties of combined cells and were located along 11 trajectories in 10 patients. The remaining movement-related cells (87 cells) were classified as voluntary cells and were located along 20 trajectories in 12 patients. Cells showing activity which could not be related either to sensory stimulation or active movement events were classified as no-response cells (384 cells).

Response patterns of movement related cells

Fig. 2 shows histograms of the activity of several different cells during the optimal response. The firing pattern changes following the baseline interval for most events in each raster, although timing of the change in firing rate may vary somewhat between events (*see* fig. 2F lowest event in the raster). In fig. 2C, there appear to be 2 intervals

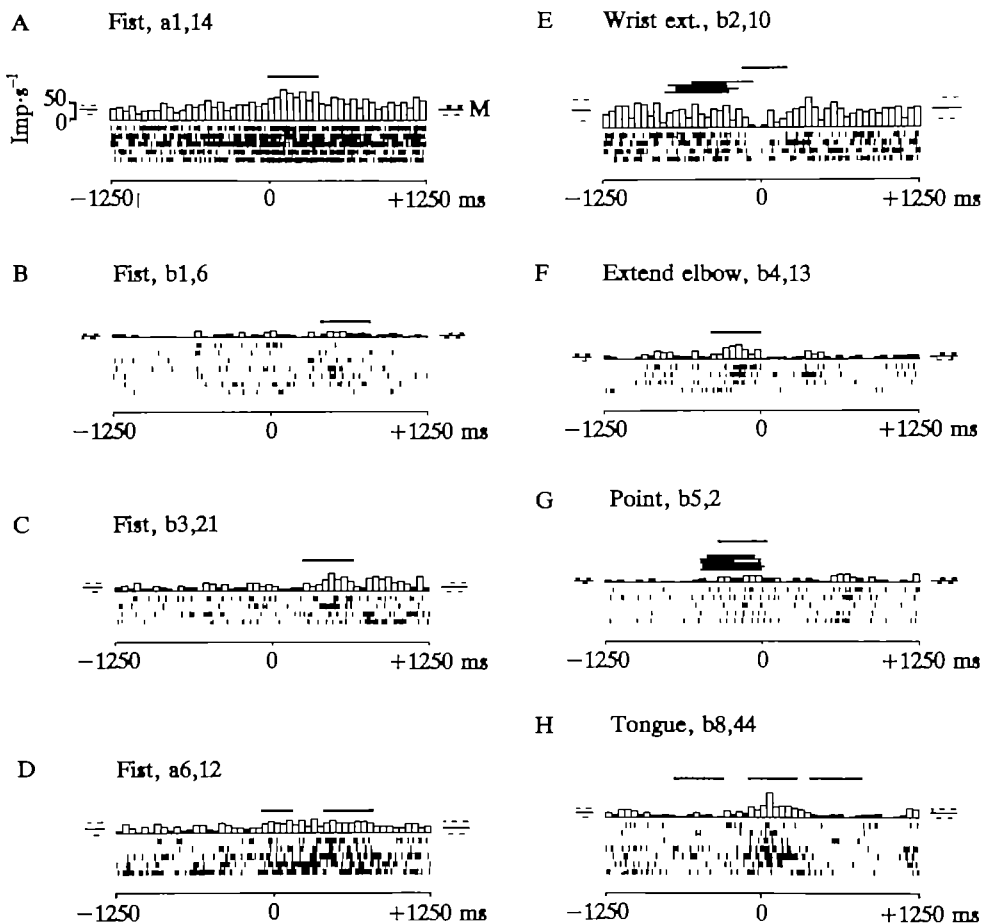


FIG. 2. Raster and histogram displays of the optimal response to active movement for 8 cells recorded in 8 different patients. Conventions are as described for fig. 1.

over which the histogram indicates an increase in the firing rate. However, the increase in firing rate over the first interval (starting at 400 ms) corresponds to a change in the firing rate during each event in the raster, while the second interval (starting at 750 ms) corresponds to a change in the firing rate during only one event (*cf.* Methods, criterion 2). Hence the first interval, indicated by the heavy line above the histogram, represented the most consistent change in firing rate.

Cells exhibited optimal responses related to the following active movements: making a fist (63 cells), extension (13 cells) or flexion (4 cells) of the wrist, flexion (1 cell) or extension (11 cells) of the elbow, pointing (6 cells), extending the tongue (8 cells) and lifting the leg (1 cell). The entire interval of altered activity occurred before the onset of EMG activity for 18% of cells having an optimal response related to making a fist, 16% of cells related to wrist extension and 0% of cells related to elbow extension. The majority of movement related cells increased their firing rate in relation to movement. Cells showing both increases and decreases in firing rate comprised 10% of the sample while those exhibiting only a decrease in firing rate comprised 2% of the sample.

Characteristics of combined cells

Fig. 3 shows an example of a combined cell which showed a strong slowly adapting response to passive elbow flexion and possibly a weak response to passive elbow extension (fig. 3B). A raster and histogram of the neuronal response during active elbow extension (fig. 3C) showed an increase (solid line) and then decrease (dashed line) in firing rate. Intervals of increased and decreased firing in the histogram corresponded to the same change in firing rate in each line of the raster. The increased firing rate was not due to activity occurring as a result of sensory input since its onset preceded the onset of movement activity by 500 ms. Note that cellular activity was related to passive and active movements about the same joint. As outlined in Table 1, all combined cells had sensory receptive fields located in the part of the body involved in the movement associated with their optimal response.

Characteristics of combined cells responding to joint movement

All combined cells responding to joint movement had their optimal responses during movements of the upper extremity. The activity of these cells was examined to determine the relationship between active and passive joint movements which were related to cellular activity. Five cells showed activity related to passive elbow flexion and active elbow extension (Cells 13, 14, 15, 17, 18). The activity of these cells was related to active and passive movements in opposite directions about the same joint.

Six cells showed activity which could be related both to the active movement of making a fist and to passive wrist dorsiflexion (Cells 6, 7, 11, 12, 16, 20). For these combined cells the relationship between the direction of active and passive joint movements was not well defined. The movement of making a fist involves cocontraction of flexors and extensors of the wrist and fingers while passive wrist extension causes stretch of wrist and finger flexors. Activity of these cells was therefore related to active and passive movements both occurring about the same joints.

A similar relationship between cellular activity during active and passive movements was seen in the 2 cells (Cells 9, 10) which were activated by loads impeding active movement but not by sensory stimulation or active movement alone. Fig. 4 displays

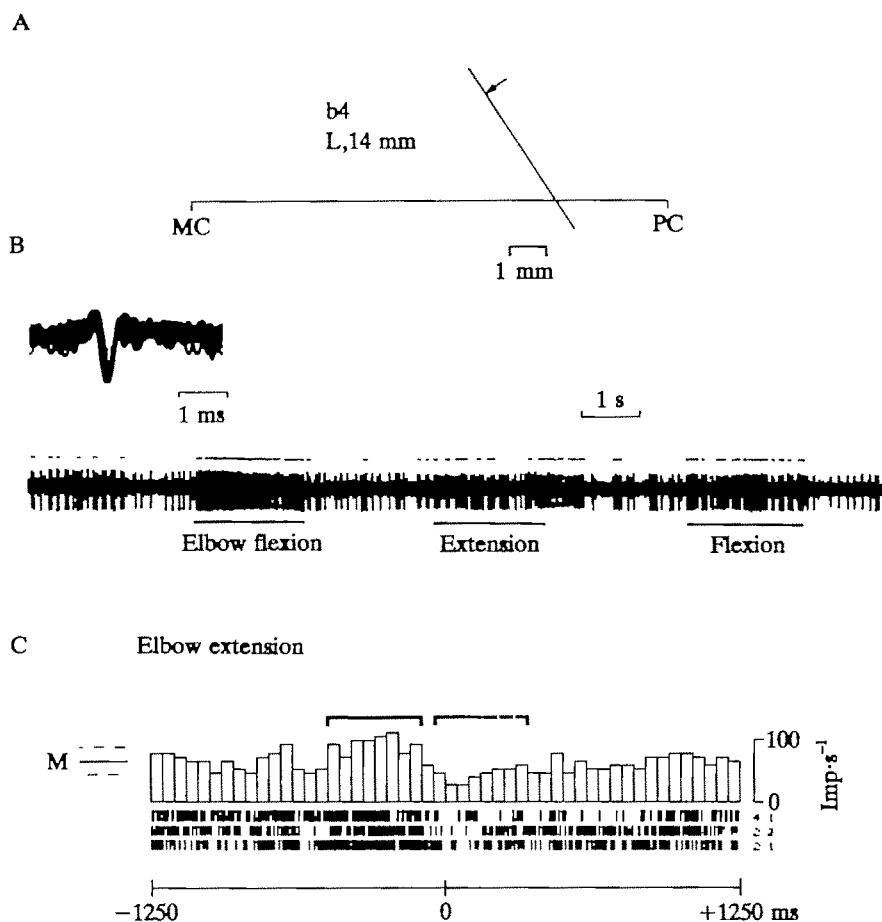


FIG. 3. Combined cell exhibiting activity related both to active movement and somatosensory stimulation. A illustrates the location of this cell (arrow) in relation to the trajectory along which it was recorded (oblique line) and the intercommissural line, indicated by the posterior commissure (PC) and the midcommissural point (MC). The patient number (b4), parasagittal plane 14 mm to the left of midline (L, 14 mm) and scale are indicated in this panel. B illustrates the response of the cell to passive elbow movement. The time scale is as indicated. Lines below the spike train in the lower panel of B indicate the approximate interval of elbow flexion and hold or extension and hold passive movements, as labelled. C shows the raster and histogram for the activity of this cell during active elbow extension. Other conventions are as described in the legend for fig. 1.

the activity of a cell (Cell 10) which responded to passive wrist flexion and active wrist extension only if the application of the external force producing flexion occurred during active dorsiflexion. This cell and the other cell with similar activity (Cell 9) were classified as combined cells. In summary, all combined cells responding to passive joint movement showed activity related to active and passive movements which occurred about the same joints.

The manual application of loads allowed flexibility in the examination of different types of active movements at operation but did not permit routine measurement of latencies

TABLE 1 PROPERTIES OF HUMAN THALAMIC COMBINED CELLS*

No	ID	L/NL	D/C	R/SA	Modality and RF	Voluntary
1	6.10.1	L	D	RA	Pressure to palm	Fist
2	6.12.1	NL	C	SA	Pressure to palm	Fist
3	4.59.6	NL	C	—	Pressure to palm	Fist
4	5.23.3	L	C	RA	Personal touch	Extend tongue
5	4.13.5	NL	C	—	Pressure to nose	Extend tongue
6	3.6.1	L	D	—	Wrist extension > flexion	Fist
7	3.8.1	L	D	—	Wrist extension and squeeze forearm flexors	Fist
8	1.5.1	L	D	—	Pressure to palm	Fist
9	3.4.1	—	D	—	—	Fist
(Increase in firing rate with increased load against fingers)						
10	1.7.1	—	D	—	—	—
(Increase in firing rate during wrist extension against resistance only)						
11	b1.33	L	D	SA	Pressure to finger and finger extension	Fist
12	b2.113	NL	D	—	Wrist extension	Fist
13	b2.119	NL	D	—	Elbow flexion inhibits	Elbow extension
14	b2.120	NL	D	—	Elbow flexion	Elbow extension
15	b2.121	NL	D	—	Elbow flexion	Elbow extension
16	b3.17	L	D	SA	Wrist extension	Fist
17	b4.13	L	D	—	Elbow flexion and squeeze triceps	Elbow extension
18	b4.17	L	D	—	Elbow flexion > extension	Elbow extension
19	b6.5	L	C	SA	Pressure to dorsum of hand	Fist
20	b2.49	NL	D	—	Wrist extension	Fist

* From left to right the columns indicate the numbers used in this paper to identify combined cells (No), the alphanumeric identifying the patient and cell number (ID), response to somatosensory stimulation either lemniscal (L) or nonlemniscal (NL); response to somatosensory stimulation, either deep or cutaneous modality (D/C), response to somatosensory stimulation either rapidly or slowly adapting (R/SA); description of modality and receptive field (Modality and RF); and the movement associated with the optimal response of the cell (Voluntary). In cases where the movement related and the sensory activities could not be evoked separately, the description of voluntary and sensory activity runs across all columns (Cells 9, 10).

and trajectories of movement in response to added loads. Cell 10 (fig. 4) demonstrated a response to application of the load occurring before the increase in EMG activity due to the added load.

Characteristics of combined cells responding to touch or pressure stimulation

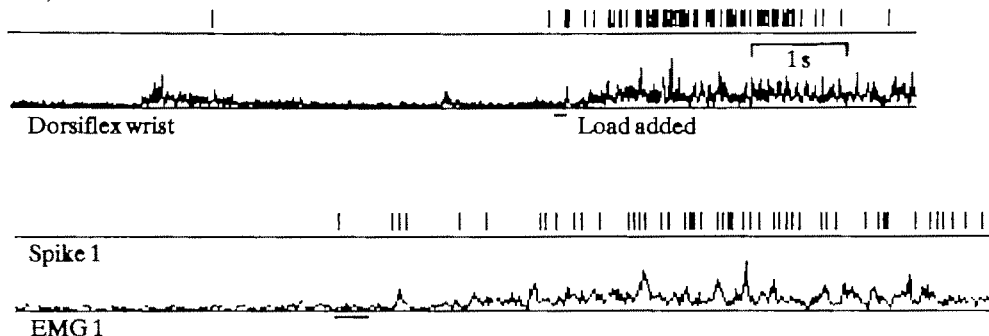
Among cells responding to cutaneous or deep touch/pressure stimuli, 5 (Cells 1, 2, 3, 8, 19) had receptive fields on the hand and responded during the active movement of making a fist. The remaining 2 units (Cells 4, 5) had receptive fields on the face and responded during active tongue movements.

Specificity of the optimal response of particular movements

The movement associated with the optimal response was identified by subjective, intraoperative examination of cellular activity during different active movements and was confirmed by constructing histograms of cellular activity during several different movements in the case of 65 cells. Histograms were constructed only for movements which were related to cellular activity during at least one repetition of the movement, based on examination of neuronal activity in the operating room. The changes in neuronal activity were evaluated for each histogram, as explained in the methods.

In fig. 5, only histograms A and B met criteria 1 and 2, and were considered to represent consistent changes in cellular activity. For each histogram satisfying criteria 1 and 2,

A a1,7



B

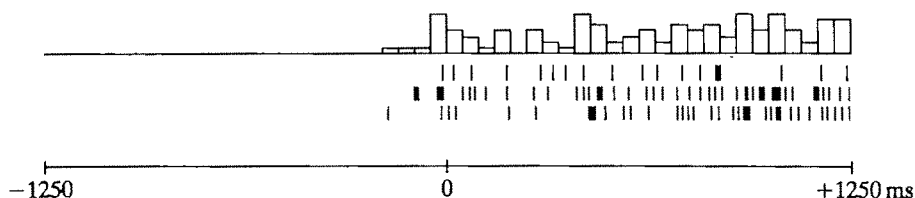


FIG. 4. Response of a thalamic cell to loads impeding active movement. In A, thalamic and finger extensor EMG activity is illustrated during active wrist dorsiflexion. A load was applied impeding voluntary wrist dorsiflexion at approximately the time of the horizontal bar labelled 'load added'. Horizontal scale of the upper panel in A is as indicated. The lower panel in A shows the same event as the upper panel at a time scale which is 2.67 times longer. B shows a raster and histogram of the activity of the cell during 3 repetitions of the increase in load.

the mean over the interval of altered firing was subtracted from the mean over the baseline interval. This difference was divided by the SEM (Snedecor and Cochran, 1967) for the baseline interval. The optimal response was then identified by the histogram for which the difference divided by the SEM was largest (histogram A in fig. 5). Histograms for cellular activity which met criteria 1 and 2 but had a lower difference divided by SEM were termed alternate responses, i.e., fig. 5B for this cell.

The results of this analysis are displayed in Table 2. An optimal response without an alternate response was found for 55 neurons. Both alternate and optimal responses were found for the remaining 10 cells. For 7 of these 10 cells, the movements associated with the optimal and alternate responses involved the same part of the body. The active movement associated with the optimal response identified in the operating room differed from that identified by analysis of multiple histograms in the case of 3 cells, 2 of which seemed to respond optimally in the operating room during wrist extension, the third during wrist flexion. Postoperative analysis of histograms identified all 3 cells as responding optimally during making a fist.

Locations of movement-related cells

Fig. 6 illustrates the relative locations of movement related cells (both combined and voluntary) with optimal responses as labelled. Trajectories lie in parasagittal planes oblique to the line joining the posterior commissure (PC) and the midcommissural point (MC),

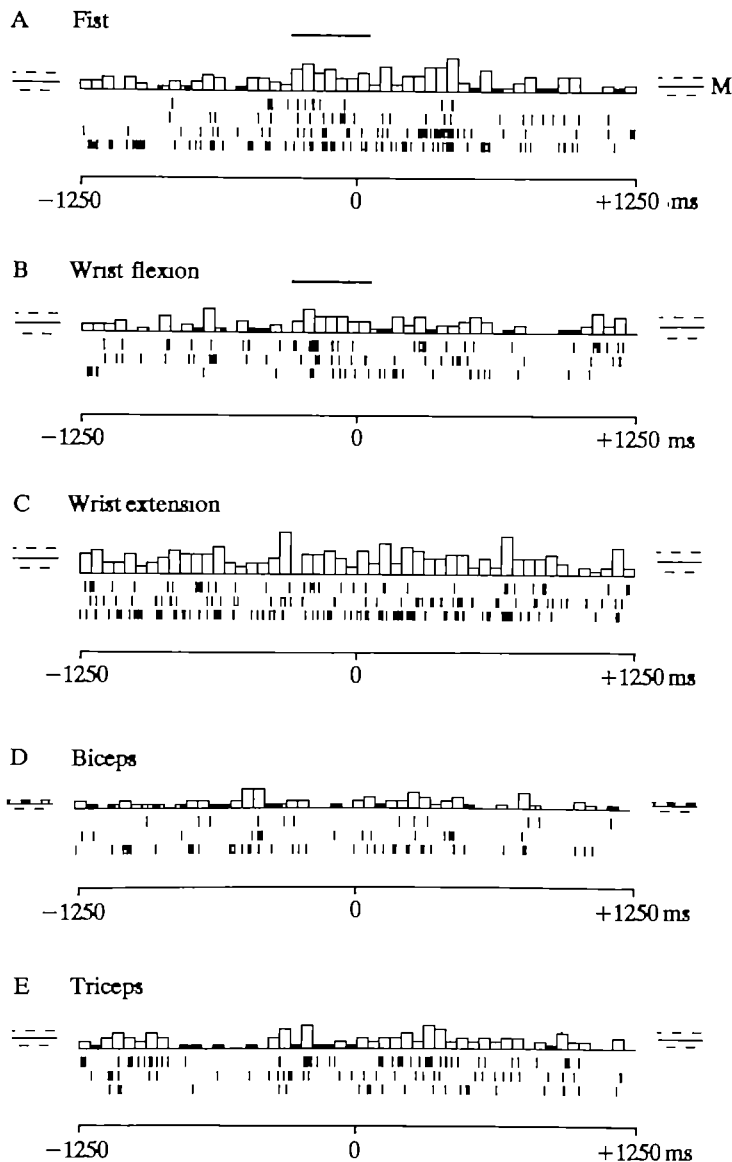


FIG. 5. Raster and histogram displays for the activity of one neuron during 5 different active movements, all cued verbally. The movement is indicated to the upper left of each histogram. Biceps and triceps indicated elbow flexion and extension, respectively. Other conventions are as described for fig. 1.

indicated in fig. 6A. Fig. 6A illustrates a trajectory in which all movement related cells had their optimal response during the same movement—making a fist. Three or more movement-related cells per trajectory were recorded in a total of 13 trajectories as detailed in Table 3. Note that the movement associated with the optimal response was the same or was related to movements of the same part of the body for the majority of cells along any trajectory.

TABLE 2 OPTIMAL AND ALTERNATE RESPONSES FOR THALAMIC CELLS WITH ACTIVITY RELATED TO ACTIVE MOVEMENT*

<i>Optimal response</i>	<i>Alternate response</i>	<i>No. of cells</i>
Tongue	—	1
Tongue	Fist	2
Fist	—	34
Fist	Wrist ext.	3
Fist	Wrist flex	3
Fist	Point	1
Wrist ext.	—	10
Wrist ext	Wrist flex	1
Wrist flex	—	4
Elbow ext.	—	3
Point	—	3

* This table indicates the results in the case of 65 cells for which histograms of cellular activity were analysed during multiple different active movements. The right-hand column indicates the total number of cells that had the pattern of optimal and alternate responses indicated in the 2 columns to the left. Cells for which only one movement was associated with a significant change in firing rate have no alternate response

In any given patient, movement related cells located in different parasagittal planes had different optimal responses. Fig. 6c illustrates data from a patient in whom cells having an optimal response associated with tongue movement were found in a plane 4 mm medial to one with cells responding optimally during elbow movements. Fig. 6d illustrates data from another patient in whom cells with activity related to hand movement were located 2 mm medial to those with activity related to elbow movement. In a third patient neurons with activity related to hand and wrist movement were located medial to those with activity related to wrist and elbow movement.

Relative somatotopic arrangement of movement-related cell and sensory cells

The results shown in fig. 6 suggest that movement-related cells are somatotopically arranged. In order to compare the somatotopic arrangement of movement-related cells with that of sensory cells, the positions of combined, voluntary and sensory cells in individual patients are shown in fig. 7.

In each case shown in fig. 7, the part of the body involved in movement associated with the activity of movement-related cells was correlated with the part of the body containing receptive fields of cutaneous sensory cells located in the same parasagittal plane. For example, in fig. 7A cells with perioral receptive fields were in the same plane as those with activity related to movements of the tongue. A similar pattern was shown by fig. 7B in which cells having digital receptive fields were located posterior to those with activity related to active finger movement, and by fig. 7C in which cells with forearm, hand and digital receptive fields were located posterior to cells with activity related to active elbow movement. These results suggest that the spatial organization of movement-related cells may be similar to that of cutaneous sensory cells.

Human thalamic cutaneous sensory cells are arranged so that the receptive field stays relatively constant for cells located in a given parasagittal plane (Lenz *et al.*, 1988b). In different parasagittal planes the receptive fields of cutaneous sensory cells follow a medial-lateral sequence from facial structures to digits, palm, forearm and upper arm.

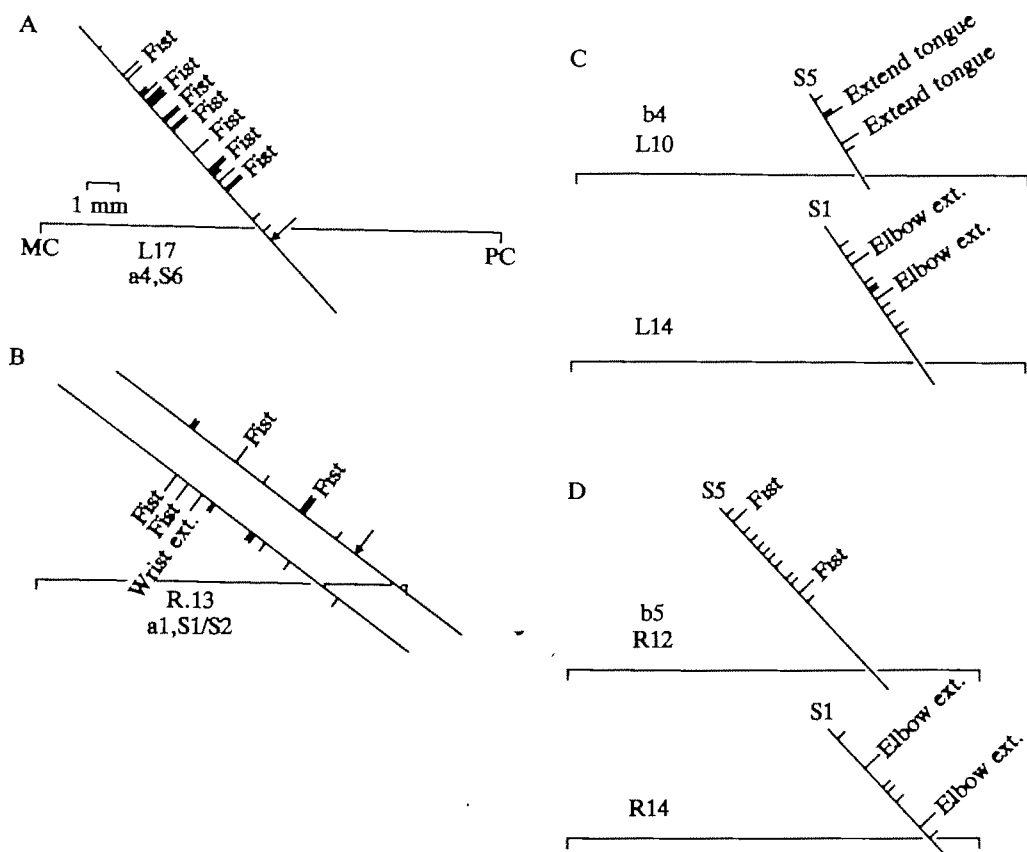


FIG. 6 Location of movement-related cells relative to the AC-PC line and the midline. The horizontal line represents the AC-PC line with the posterior commissure (PC) and the midcommissural point (MC) as indicated in A. The oblique line represents the trajectory followed by the microelectrode. The lines at right angles to the trajectory represent the locations of cells which had their optimal response during the movement indicated. The shorter lines at right angles to the trajectory indicate the position of cells which did not change their firing rate during active movement. Single trajectories in individual patients are shown in A and B, while trajectories in two different parasagittal planes are shown in C and D. The most anterior cell with a lemniscal response to cutaneous stimulation along any given trajectory is indicated by the arrow. The scale is given in A. Other conventions are as described for fig. 3.

Figs 6C, D, and 7 suggest that movement-related cells tend to be somatotopically arranged in a similar pattern so that cells with activity related to facial movements were located medially while those related to hand and arm were located laterally.

Relative locations of different cell types

The locations of voluntary and combined cells was first determined relative to the AC-PC line and the location of sensory cells (fig. 8). Data from different patients have been pooled depending on whether the majority of movement-related cells in a given parasagittal plane had optimal responses associated with movements of face (fig. 8A), hand and wrist (fig. 8B) or elbow and shoulder (fig. 8C).

Data were pooled by shifting results in an individual patient along the AC-PC line

TABLE 3 OPTIMAL RESPONSES FOR MOVEMENT-RELATED CELLS LOCATED ALONG THE SAME TRAJECTORIES*

<i>Tongue</i>	<i>Fist</i>	<i>Wrist</i>	<i>Elbow</i>	<i>Shoulder</i>	<i>NR</i>
—	2	1	—	—	7
—	3	—	—	—	4
—	3	—	—	1	3
1	2	—	—	2	12
—	16	—	—	—	4
3	—	—	—	—	1
—	3	—	—	—	9
—	4	—	—	—	9
—	4	4	—	—	4
—	4	2	—	—	5
—	4	3	3	—	9
2	1	—	—	—	6
—	4	—	—	—	17

* The table indicates the number of cells having optimal responses during a given movement for all cells located along trajectories with 3 or more movement-related cells. Each row indicates optimal responses observed along a single trajectory. Movements related to the optimal responses are indicated by the part of the body or the joint involved in the movement. The number in the NR column indicates the number of cells along that trajectory for which no movement-related activity could be identified.

so that the region containing sensory cells having a lemniscal response pattern (lemniscal sensory cells) was aligned in all patients. All trajectories in a given plane of each patient were shifted so that the most anterior lemniscal sensory cell in the more posterior trajectory was aligned with the vertical line in fig. 8. When the data are pooled in this way, some lemniscal sensory cells in the more anterior of 2 trajectories in an individual patient are located anterior to the vertical line (*see* fig. 2B). We assumed that the vertical line approximated the anterior border of the principal sensory nucleus (Vc).

Fig. 8 demonstrates that combined and voluntary cells were found anterior to cutaneous sensory cells. When movement-related cells and sensory cells were found in separate trajectories, the most posterior movement-related cell occasionally lay posterior to the most anterior cutaneous sensory cell (*see* fig. 8A). Combined cells were sometimes located posterior to the most anterior deep sensory cell in the same trajectory as illustrated in fig. 8c. Three cells, termed auditory cells, responded at short latency to sudden loud noises and were located posterior to cutaneous sensory cells located along the same trajectories, as illustrated in fig. 7c.

As suggested by examination of fig. 8, the mean vertical distance of combined cells above the AC-PC line was less than that of voluntary cells ($t = 2.03$, $df = 74$, $P < 0.025$). The mean distance of combined cells anterior to the vertical line in fig. 8 was not significantly different from that of voluntary cells ($t = 0.016$, $df = 74$, $P > 0.65$). Fig. 8 demonstrates that sensory cells responding to stimulation of muscle, joint and tendon (deep sensory cells) were usually located anterior to cutaneous sensory cells (Lenz *et al.*, 1988b).

Nuclear locations of different cell types

The location of combined cells was next estimated relative to presumed nuclear boundaries by plotting cellular position on sagittal maps of the human thalamus modified

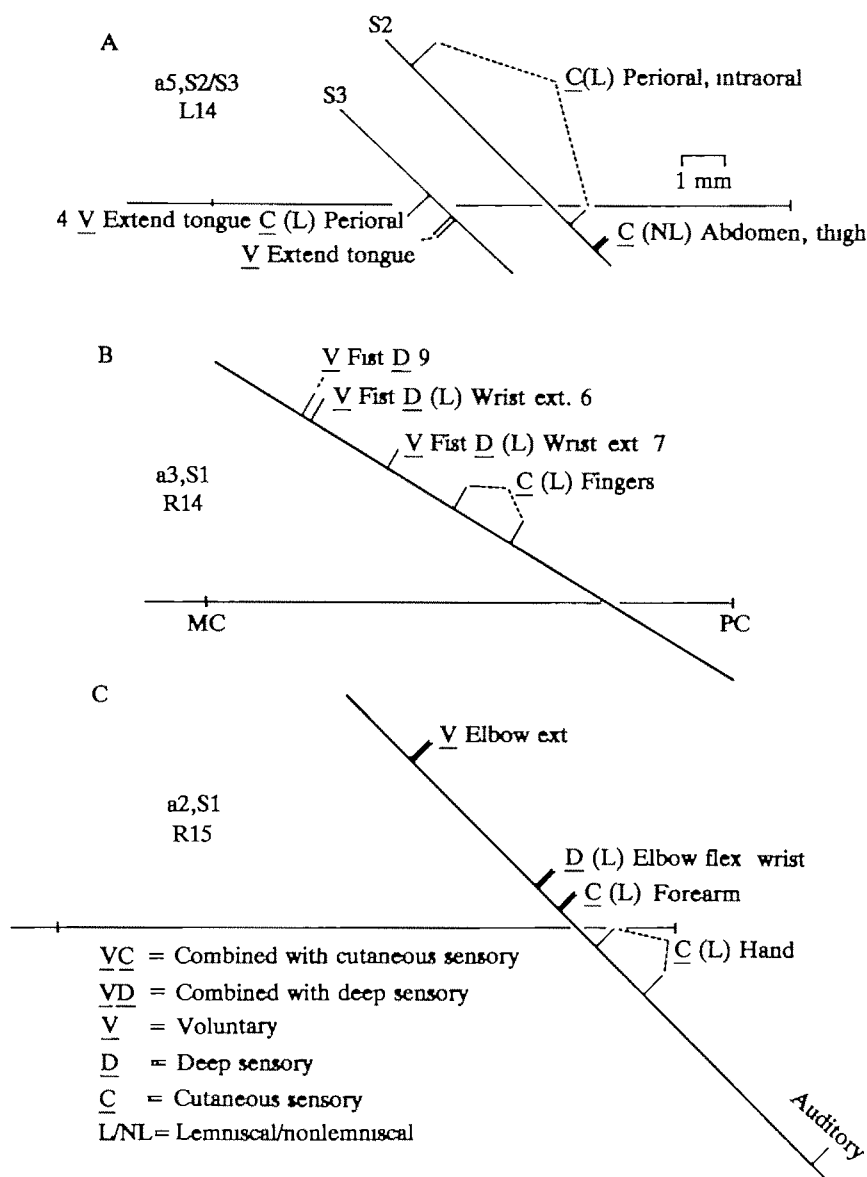


FIG. 7. Relative anatomical locations of voluntary, sensory and combined cells. The horizontal line is the AC-PC line with the posterior commissure (PC) and the midcommissural point (MC) as indicated in B. Short lines perpendicular to the trajectories indicate the locations of identified cells. Brackets enclose segments of different trajectories where all cells showed the activity indicated by the label at the apex of the bracket. The underlined letters in the label indicate whether the cell showed activity related to voluntary movement (V) and/or sensory stimulation (deep/cutaneous—D/C). Following each underlined letter are a few words indicating either the nature of the optimal response during voluntary movement or receptive field for the response to sensory stimulation. The nature of the sensory response (lemniscal/nonlemniscal—L/NL) is specified in brackets following the underlined letter indicating a response to somatosensory stimulation. The cell types indicated by different combinations of these symbols are given in the lower left-hand corner of C. The scale is indicated in A.

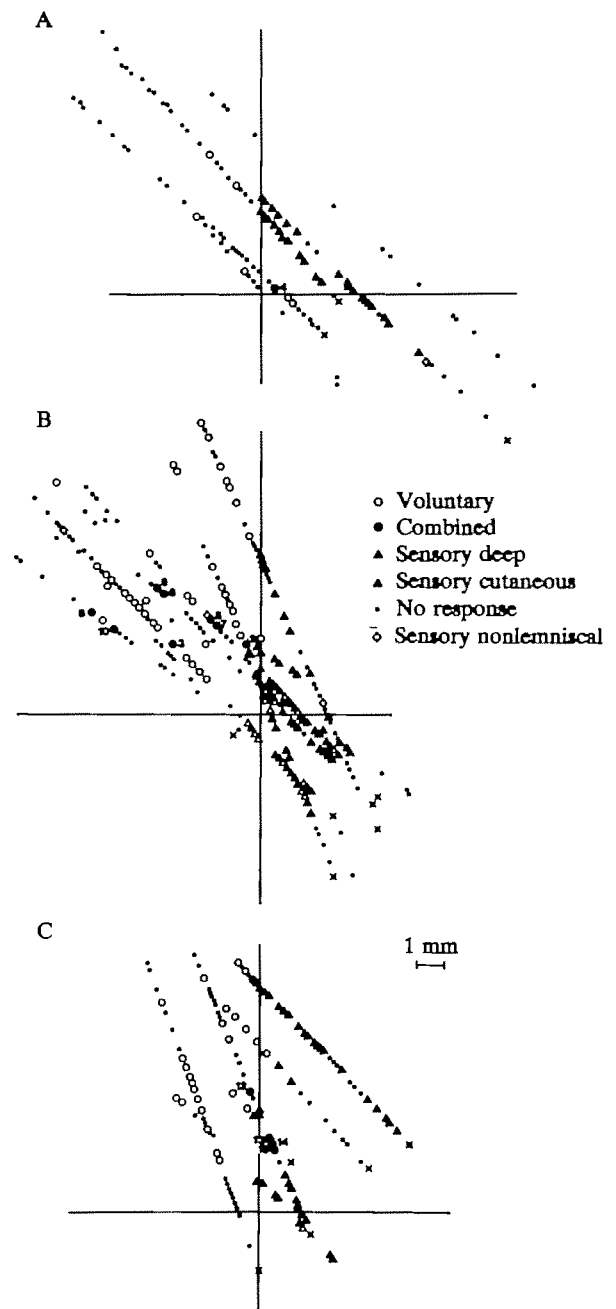


FIG. 8. Relative locations of identified cells pooled from several patients. Results from different parasagittal planes in different patients have been grouped according to the movement associated with the optimal response of movement-related cells occurring in that plane (A, facial movements; B, hand and wrist, C, elbow and shoulder). The AC-PC line is represented by the horizontal line in each panel and the results from various planes in different patients have been shifted along the AC-PC line until the most anterior lemniscal sensory response in the more posterior trajectory for each patient was aligned with the vertical line. Symbols representing the different types of cells are indicated in the fig. to the right of B. Cells without activity related to either sensory stimulation or active movement were termed no-response cells, represented by dots. Numbers adjacent to the combined cells correspond to those listed in the left-hand column (No) of Table 1. The 'x' at the end of some trajectories indicates the point at which neuronal action potentials could no longer be recorded.

by stretching or shrinking the atlas diagram (Schaltenbrand and Bailey, 1959) to match the AC-PC distance in the patient (Hawrylyshyn *et al.*, 1976). These data, which are listed in Table 4, suggested that the largest number of combined and deep sensory cells were located in ventralis caudalis (Vc) while the largest number of voluntary cells were

TABLE 4 NUCLEAR LOCATION OF COMBINED DEEP SENSORY AND VOLUNTARY CELLS BY PRESUMED NUCLEUS OF VENTRAL THALAMUS*

	<i>Combined</i>	<i>Deep sensory</i>	<i>Voluntary</i>
Voa	—	9	1
Vop	4	5	21
Vim	7	44	49
Vc	9	47	16
Vcpor	—	9	—
WM	—	4	—
Total	20	118	87

* The columns indicate different cell types; rows indicate thalamic nuclei. Entries are in the number of cells in the nucleus indicated. Voa = ventralis oralis anterior; Vop = ventralis oralis posterior; Vim = ventralis intermedius; Vc = ventralis caudalis; Vcpor = ventralis caudalis portae, WM = white matter below the lower border of thalamus.

located in Vim. The wide dispersion of different cell types might have been due to imprecision in the stereotactic atlas (Schaltenbrand and Bailey, 1959) and in the radiological localization (Kelly *et al.*, 1978) or to normal anatomical variation. These results therefore confirmed the necessity for physiological determination of the surgical target by demonstrating that the radiological determination is only an estimate of nuclear location.

Voluntary cells tended to be located in nuclei anterior to those containing cells that responded to sensory stimulation (sensory/combined cells). Pairwise testing of proportions of different cell types (voluntary, combined, deep sensory) located in Vc and Vim was carried out. Voluntary cells were more likely to be located in Vim than were combined cells ($P < 0.025$, χ^2) or deep sensory cells ($P < 0.005$). The proportion of combined cells in Vim was not significantly different from that of deep sensory cells.

DISCUSSION

Technical considerations

The use of verbal commands proved to be the only feasible method for cueing several different active movements within the time constraints imposed by the operative procedure. This technique does not allow examination of neuronal firing related to specific cues for either motor preparation or instruction to move. Nevertheless, the movement trigger used in constructing histograms is a reliable temporal indicator of the onset of movement. Furthermore, some studies in nonhuman primates suggest that rasters of thalamic activity may be better aligned when the histogram is triggered by the onset of movement than by precise signals to move (*see* fig. 7, Strick, 1976b; MacPherson *et al.*, 1980).

Previous reports have used many different approaches to demonstrate thalamic neuronal activity related to active movement in man. Thalamic activity has been recorded by different techniques (reviewed by Lenz *et al.*, 1988a) and has been analysed by examining loudspeaker and oscilloscope output of thalamic responses to single repetitions (Jasper and Bertrand, 1966; Crowell *et al.*, 1968; Bertrand, 1972) and to multiple repetitions

of a voluntary movement (Siegfried *et al.*, 1969; Li and van Buren, 1972; Hongell *et al.*, 1973; Fukushima and Schramm, 1975). Analysis of single trials has been performed by counting the number of action potentials within a fixed sampling interval so that a change in the number of counts per sampling interval represented a change in thalamic activity (Umbach and Ehrhardt, 1965; Raeva, 1972, 1977, 1986; Raeva and Livanov, 1975). The technique of raster and histogram analysis has not previously been applied to the study of human thalamic activity related to active movement.

Characteristics of human and monkey neuronal activity during active movement

Raeva (1986) has published the most detailed account of human thalamic activity related to active movement. Of recording sites in VL (defined as equivalent to Voa, Vop and Vim), 4% showed activity occurring in relation to the verbal command to move, 66% to the movement and 12% to maximal contraction. At other sites the spectral power of thalamic activity at tremor frequency was increased or decreased during voluntary movement. Two-thirds of single units were found to be excited in relation to voluntary movements, while the remainder were either inhibited or exhibited a complex pattern of excitation and inhibition (Raeva, 1972; *see also* Umbach and Ehrhardt, 1965). Other workers have suggested that neuronal activity is more frequently increased than decreased in relation to voluntary movement (Crowell *et al.*, 1968; Hongell *et al.*, 1973). There are numerous reports of isolated cells or recording sites at which activity increases (Umbach and Ehrhardt, 1965; Jasper and Bertrand, 1966; Siegfried *et al.*, 1969; Bertrand, 1972; Fukushima and Schramm, 1975) or decreased (Umbach and Ehrhardt, 1965; Siegfried *et al.*, 1969) in relation to active movements.

The present results demonstrate that the movement-related activity of single units may involve increases or decreases in firing rate. During periods of tremor in parkinsonian patients, many of these cells demonstrated activity at a tremor frequency that was correlated with EMG activity during tremor (Lenz *et al.*, 1988c). In combination, these results demonstrate that a population of human thalamic cells show activity which may be related both to involuntary and voluntary movements (Lenz *et al.*, 1985).

Specificity of neuronal activity for particular active movements

The present results suggest that most movement-related cells changed their firing pattern preferentially in relation to the execution of a particular movement. The specificity of thalamic neuronal responses to particular voluntary movements has infrequently been examined in the past. Hongell *et al.* (1973) found that thalamic multiple unit activity at 10 sites changed in relation to one particular movement, while at 6 other sites a change was seen during two or more movements. Crowell *et al.* (1968) observed 11 units whose activity increased in advance of specific voluntary movements and 10 whose activity decreased in relation to multiple voluntary movements.

The activity of thalamic cells related to active movements has been studied in chronic primate preparations by several groups (Evarts, 1970, 1971; Joffroy and Lamarre, 1974; Strick, 1976b; Horne and Porter, 1980; MacPherson *et al.*, 1980; Allum *et al.*, 1983). In these reports, monkeys responded to visual (Evarts, 1970, 1971; Strick, 1976b; MacPherson *et al.*, 1980; Allum *et al.*, 1983) and somatosensory (MacPherson *et al.*, 1980) stimulation by performing an isometric task (Allum *et al.*, 1983), a movement involving either several forelimb joints (Strick, 1976b; Horne and Porter, 1980) or a

movement involving one forelimb joint with other joints acting as stabilizers (Evarts, 1970, 1971; MacPherson *et al.*, 1980). Cellular responses were defined by examination of histograms, rasters or both. Neurons altered their firing rate in relation to cues for active movement (Strick, 1976b; MacPherson *et al.*, 1980) or to the movement itself (Joffroy and Lamarre, 1974; Strick, 1976b; Horne and Porter, 1980; Allum *et al.*, 1983).

Directionally specific activity, defined as excitation during joint movement in one direction and inhibition during movement in the opposite direction, has been observed only in a limited number of cells in the thalamus of nonhuman primates (23%, MacPherson *et al.*, 1980; 34%, Strick, 1976b). The majority of cells responded with either excitation or inhibition during both directions of movement and so were not directionally specific. The activity of these latter cells may have been related to synergistic muscle groups activated during both directions of movement (MacPherson *et al.*, 1980). Observations of videotapes recorded during complex movements (Horne and Porter, 1980) and of incidental movements occurring during the movement paradigm (Strick, 1976b; Horne and Porter, 1980) have suggested that the activity of many cells can be related to performance of an isolated movement. The results of the present study are consistent with the suggestion that the activity of movement related cells is specific for particular active movements. This specificity may be similar to that seen in the activity of primate precentral cortical cells which exhibit responses only during one direction of movement about a single joint (Murphy *et al.*, 1982; Evarts *et al.*, 1984; Wise, 1985).

Locations of neurons

The locations of primate thalamic neurons with activity related to active movement have been anatomically confirmed (Evarts, 1971; Strick, 1976b; Horne and Porter, 1980; MacPherson *et al.*, 1980) in the ventrolateral (VL) and ventroposterolateral, pars oralis (VPLo) nuclei (Olszewski, 1952). By our best estimate, the majority of human thalamic neurons with activity related to voluntary movement are located in Vim and Vop (*see* Table 4). On the basis of cytoarchitectonic criteria, immunohistochemical studies (Hirai and Jones, 1989) and afferent and efferent connections, the nuclei in nonhuman primates (Olszewski, 1952) which correspond to those in man (Hassler, 1982) are VPLo to Vim, VL (consisting in part of VLo, VLc, and X) to Vo (consisting of Voa and Vop), VPLc to Vc (Mehler, 1971; van Buren and Borke, 1972; van Buren *et al.*, 1976; Hassler *et al.*, 1979; Asanuma *et al.*, 1983a; *see also* discussion of nomenclature in Percheron, 1977; Schaltenbrand and Walker, 1982; Hirai and Jones, 1989). The present results therefore suggest that human movement related cells are located in nuclei (Vim and Vop) equivalent to those where movement related cells are located in nonhuman primates (VPLo and VL).

Lamellar organization of human thalamus

The specificity of thalamic movement-related cells for particular active movements (fig. 5, Table 2) forms the basis for a discussion of the somatotopic organization of these cells. In the present study, cells with activity related to movement of a particular part of the body were found in the same parasagittal plane in individual patients. Results in nonhuman primates suggest that neurons with activity related to arm movements may (Strick, 1976b; Horne and Porter, 1980) or may not (MacPherson *et al.*, 1980) be found in a restricted mediolateral thalamic location.

Certainly, anatomical evidence suggests that the monkey VL thalamus may exhibit a lamellar pattern of somatotopic organization (Thach and Jones, 1979) similar to that found in the ventrobasal complex of monkeys (Jones and Friedman, 1982; Kaas *et al.*, 1984) and man (Lenz *et al.*, 1988b). Such a lamellar pattern has been demonstrated by retrograde labelling of thalamocortical neurons (Strick, 1976a; Kievit and Kuypers, 1977; Hendry *et al.*, 1979; Jones *et al.*, 1979; Asanuma *et al.*, 1983b; Schell and Strick, 1984), anterograde labelling or degeneration of corticothalamic neurons (Künzle, 1976; Jones *et al.*, 1979) and anterograde labelling of cerebellothalamic neurons (Kalil, 1981; Thach and Jones, 1979; Asanuma *et al.*, 1983b, c). Anterograde transport and degeneration studies of the pallidothalamic connection (Nauta and Mehler, 1966; Kim *et al.*, 1976; DeVito and Anderson, 1982) have not addressed the issue of lamellar organization. The present results therefore represent physiological evidence that cells with optimal responses related to specific movements may be grouped in a lamellar pattern similar to that suggested by the anatomical studies in monkeys.

Somatotopic arrangement of movement-related cells

The lamella might be considered as the 'unit of isorepresentation' (Kaas *et al.*, 1972, 1984) which forms the basis for somatotopic organization of movement related cells. The present results suggest a mediolateral somatotopic arrangement of lamellae in which facial movements are represented medially and shoulder movements are represented laterally. Such an arrangement would be similar to that of human cutaneous sensory cells (Lenz *et al.*, 1988b). Therefore it may be that the same basic somatotopic organization applies to both sensory and motor portions of the human ventral thalamic nuclear group.

The mediolateral somatotopic sequence of movement-related cells suggested by this report is consistent with anatomical studies in nonhuman primates. Primate thalamo-cortical connections are arranged so that the medial motor cortex, representing the leg, receives projections from lateral VPLo while lateral motor cortex, representing the arm, receives projections from medial VPLo (Walker, 1934; Strick 1976a; Jones *et al.*, 1979). It has been suggested that there are somatotopically arranged connections to thalamus from cerebellum (Perry and Thach, 1979; Asanuma *et al.*, 1980, 1983b; Brooks and Thach, 1981) and pallidum (Carpenter *et al.*, 1976; Nauta, 1979; DeLong and Georgopoulos, 1981; DeVito and Anderson, 1982; Schell and Strick, 1984).

Somatotopic organization of movement-related cells in VPLo was found by some but not all physiological studies of active movements in intact monkeys. Evidence from primates performing upper limb movements suggests that the thalamic neurons responding during arm movements are located in a narrow parasagittal plane lateral to that containing cells responding during incidental facial movements (Strick, 1976b; Horne and Porter, 1980). However, the wide dispersion of neurons related to arm movements in another primate study is inconsistent with mediolateral somatotopic segregation of movement related cells (MacPherson *et al.*, 1980).

Two clinical studies have examined the possibility of somatotopic organization of Vop and Vim. Uno *et al.* (1967) found that scalp potentials evoked by stimulation of Vim in man were maximal over lateral motor cortex in response to stimulation of presumed medial Vim and maximal over medial motor cortex in response to stimulation

in presumed lateral Vim, implying medial to lateral thalamic somatotopy. Ohye *et al.* (1977) also found evidence for medial to lateral somatotopy by correlating the sites of thalamic stimulation with the body parts in which tremor arrest occurred. The somatotopic organization of movement related cells reported here is therefore consistent with the pattern suggested by anatomical and physiological studies in nonhuman primates and by stimulation evoked effects in man. In turn, the relationship between somatotopic organization of sensory and motor thalamus may prove useful in the localization of stereotactic targets for the relief of tremor (Tasker *et al.*, 1982; Lenz *et al.*, 1988a).

Sensorimotor properties of human thalamus

Regions of thalamus having both motor and sensory functions are suggested by reports of thalamic sites where multiple units responded to sensory stimulation and where bipolar stimulation at 0.1 to 1.5 mA evoked motor effects consisting of muscle twitches (Albe-Fessard, 1973; Ohye and Narabayashi, 1979) and alteration in tremor (Ohye and Narabayashi, 1979). The motor and sensory effects were linked so that '... such electrical stimulation produced a small movement in a localized part of the contralateral extremity more or less involving the same receptive field' (Ohye and Narabayashi, 1979). Since the anatomical regions sampled by multiple unit recordings and stimulated to produce movement are uncertain (Jankowska *et al.*, 1975; Ranck, 1975), these sensory and motor effects might have been produced by regions of thalamus which are separate but adjacent. Alternatively, these results might be explained by recordings from and stimulation of combined cells with activity related to passive and active movements about the same joints.

Human thalamic neurons with activity related to both passive and active movements have been described previously (Jasper and Bertrand, 1966; Raeva, 1986). The movement-related activity of these cells was attributed to sensory stimulation occurring as a result of movement. Jasper and Bertrand (1966) published a detailed account of the activity of a single neuron which responded during passive wrist dorsiflexion and clenching of the fist (fig. 10, Jasper and Bertrand, 1966). Since thalamic and EMG activity during active movement were not displayed, it is possible that movement-related activity preceded EMG onset and was not solely produced by sensory stimulation resulting from movement. This cell might therefore have shown activity similar to cells, 6, 7, 11, 12, 16 and 20 (Table 1). The present results demonstrate that the movement-related activity of these cells is at least partially related to active movement and does not occur exclusively as a result of somatosensory stimulation.

Sensory inputs to movement-related cells in nonhuman primates

Studies in chronic primate preparations have identified cells in VPLo and VL which were activated in relation both to sensory stimulation and active movement (Strick, 1976b; Horne and Porter, 1980; MacPherson *et al.*, 1980). The percentage of movement-related cells in this area responding to somatosensory stimulation was reported at 25% (Strick, 1976b) to 43% (MacPherson *et al.*, 1980). In some studies (Strick, 1976b; MacPherson *et al.*, 1980) responses were found to be indistinct, variable and related to deep pressure or to rapid joint movement. Others reported that many movement-related cells in VPLo responded to sensory stimulation with lemniscal response patterns as evidenced by cutaneous receptive field sizes as small as 1 mm² (Horne and Porter, 1980).

These same groups have also studied the response of movement-related cells to motor perturbations interfering with active movement. Increases in firing rate (load compensating activity) were reported in 28 of 160 motor cells (Strick, 1976*b*) and in 'numerous' motor cells (MacPherson *et al.*, 1980). Horne and Porter (1980) found motor cells did not respond to torque loads interfering with the complex multijoint movements used in that study. However, torque loads were not sufficient to evoke an EMG response and may not have been large enough to evoke a thalamic response (R. Porter, personal communication). Methodological differences aside, studies of chronic primate preparations have identified numerous movement-related cells which responded to somatosensory stimulation with either nonlemniscal (Strick, 1976*b*; MacPherson *et al.*, 1980) or lemniscal response patterns (Horne and Porter, 1980). The load compensating activity of these cells is similar to that seen in the present results (Cells 9, 10).

Responses to somatosensory stimulation observed in movement-related cells of chronic primate preparations (Strick, 1976*b*; Horne and Porter, 1980; MacPherson *et al.*, 1980) have been attributed to inadvertent voluntary reaction to sensory examination (Wiesendanger and Miles, 1982). This mechanism is unlikely to explain the present results for two reasons. First, the sensory response was often obvious on examination of a single trial whereas histograms were required to confirm movement-related activity (*see* fig. 3). It is therefore unlikely that weak movement-related activity could mimic the stronger sensory response. Secondly, since patients did not have to be trained to relax during sensory examination (*see* Horne and Porter, 1980), inadvertent voluntary reaction to somatosensory examination was uncommon.

The presence of sensory input to VPLo thalamus is also demonstrated in acute primate preparations. Cells responding to somatosensory stimulation with lemniscal response patterns have been found in both ventralis posterolateralis, pars caudalis (VPLc) and VPLo (Loe *et al.*, 1977; Horne and Tracey, 1979; Lemon and van der Burg, 1979; Maendly *et al.*, 1981). Others have found cells with lemniscal and nonlemniscal sensory responses, respectively, in VPLc and VPLo (Poggio and Mountcastle, 1963; Jones and Friedman, 1982). In summary, somatosensory input to human movement-related cells is similar to that identified in nonhuman primate preparations, both acute and chronic. Therefore, the present results can be interpreted by exploiting similarities between humans and nonhuman primates (Hirai and Jones, 1989), since afferent and efferent connections of thalamus are more completely studied in the latter.

Afferent and efferent connections of thalamic movement-related cells

Anatomical studies have suggested a number of sources for sensory afferents to VPLo and Vim, respectively, in nonhuman primates and man. The spinothalamic tract, including a weak contribution from low threshold muscle afferents (Foreman *et al.*, 1979), terminates partly in VPLo of nonhuman primates (Boivie, 1979; Berkley, 1980, 1983; Tracey *et al.*, 1980) and in Vim of man (Bowsher, 1957; Mehler, 1962, 1966). However, recent evidence suggests that the spinothalamic termination may not be in that region of VPLo which projects to motor cortex (Greenan and Strick, 1986). The dorsal column-medial lemniscus system, including the external cuneate system, may terminate partly in VPLo (Boivie, 1978, 1980; Berkley, 1983) although other anatomical studies have found that the medial lemniscus terminates in VPLc alone (Tracey *et al.*, 1980; Kalil, 1981). Similarly, anatomical studies in chimpanzees (van Buren and Borke, 1972) and

man (Nauta and Mehler, unpublished observations quoted in Mehler *et al.*, 1960) indicate that medial lemniscus may (Mehler *et al.*, 1960) or may not (van Buren *et al.*, 1976) terminate partly in Vim. Finally, the deep cerebellar nuclei project heavily to VPLo in nonhuman primates (Thach and Jones, 1979; Kalil, 1981; Asanuma *et al.*, 1983a, b; Berkley, 1983) and Vim in man (Nashold and Slaughter, 1969; van Buren and Borke, 1972, 1976; cf. Mehler, 1971) and contain cells which respond weakly to somatosensory stimulation in nonhuman primates (Brooks and Thach, 1981). Thus spinothalamic, dorsal column and cerebellar afferents may contribute sensory afferents to cells with activity related to both somatosensory stimulation and active movement.

Cells in VPLo which respond to sensory stimulation may provide sensory input to motor cortex (Asanuma *et al.*, 1980), since VPLo projects to motor cortex (*see*, e.g., Schell and Strick, 1984). Alternatively, sensory input may be relayed to motor cortex via VPLc and postcentral cortex (Malis *et al.*, 1953; Strick, 1976b; Asanuma *et al.*, 1980; Jones and Porter, 1980).

Many aspects of the present results are consistent with studies in nonhuman primates. Similarities between humans and nonhuman primates may be useful in the interpretation of abnormal activity recorded in patients with movement disorders and in primate models of these disorders. For example, many combined and voluntary cells in parkinsonian tremor patients showed activity correlated with EMG during tremor (Lenz *et al.*, 1985, 1988c). Interpretation of this tremor-related activity is based on the assumption that the pathways afferent and efferent to combined and voluntary cells are the same as those of primate movement-related cells with similar functional properties and locations (Lenz *et al.*, 1985). Analysis based on this assumption has proven useful in identifying human thalamic cells which might be involved in the generation of tremor (Lenz *et al.*, 1985).

The mechanism of different types of tremor can be differentiated by the extent to which each type is dependent upon sensory feedback through stretch reflex arcs (Stein and Lee, 1981; Marsden, 1984). Therefore, studies of 'tremor cell' activity in cells classified by the presence (sensory/combined cells) or absence of sensory input (voluntary/no response cells) may help define the role of sensory processes in the generation of parkinsonian tremor.

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STRIATONIGRAL DEGENERATION

A CLINICOPATHOLOGICAL STUDY

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SUMMARY

The clinical and pathological features of 10 cases of striatonigral degeneration are described: 5 were misdiagnosed in life as Parkinson's disease. Retrospectively, helpful early pointers to the diagnosis in these cases included unexplained falls, autonomic dysfunction, absence of rest tremor and failure to respond to L-dopa, but these were not always present. The pathological diagnosis could not be excluded on macroscopic examination of the striatum. Relative preservation of the putamen occurred in the 4 patients who benefited from L-dopa. The caudate nucleus was involved in all cases and there was no sparing of the large striatal neurons. In mild cases, involvement of the putamen was confined to its posterior two-thirds, dorsolaterally. With increasing severity this extended in a dorsal to ventral and posterior to anterior direction. Seven of the cases had evidence of olivopontocerebellar damage, but only 2 of these had clinical evidence of cerebellar disease. Correlation was found between the neuronal counts in caudate:putamen, striatum:nigra compacta, globus pallidus:nigra compacta, nigra compacta:locus coeruleus. The most severely involved part of the substantia nigra pars compacta was the ventrolateral zone, which projects to the dorsal putamen, the earliest site of striatal disease.

INTRODUCTION

The term striatonigral degeneration (SND) was first used by Adams and colleagues (1961, 1964, 1986) to describe 4 patients with a parkinsonian syndrome who at postmortem had marked nerve cell loss, gliosis and pigmentation of the putamen and variable cell loss and gliosis of the caudate and globus pallidus with neuronal fall-out in the substantia nigra. The disorder is often clinically indistinguishable from Parkinson's disease (PD) so its precise frequency is unknown. Before the report of Adams *et al.* (1961), similar cases were described as having olivopontocerebellar atrophy (OPCA), which is still the favoured term by many clinicians and pathologists when associated cerebellar involvement is present. The all-embracing term multiple system atrophy (MSA) has been suggested by others (Graham and Oppenheimer, 1969) to emphasize the undoubted clinical and pathological overlap between three clinical groups of patients presenting with cerebellar ataxia (OPCA), a parkinsonian syndrome (SND) or autonomic symptoms (progressive autonomic failure). The advantage of this term is that initially pure clinical examples of the three subtypes may go on to acquire symptoms seen with the other two and even if they do not they often have evidence at postmortem of multisystem involvement. Furthermore, in the familial form considerable clinical heterogeneity occurs in some kinships. Although the pathology appears to be specific, there is no characteristic neuronal inclusion and identical cases have been reported secondary to adrenoleukodystrophy (Ohno *et al.*, 1984) and mitochondrial encephalomyopathy

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(A. E. Harding, personal communication). The clinical diagnosis of SND cannot be made with certainty in life, but a number of helpful pointers may enable it to be suspected. These include failure to respond to L-dopa, rapidly progressive symptoms and absence of rest tremor at presentation.

In order to clarify the clinical and pathological features of SND we have carried out a detailed morphological study on 10 patients, 5 of whom were diagnosed by neurologists as having PD. We have also correlated the degree of nerve cell loss in the putamen with the patients' clinical response to L-dopa.

MATERIAL AND METHODS

Pathological material was taken from the UK Parkinson's Disease Society Brain Bank. At the time of the study, 22% of the 73 brains collected were pathologically diagnosed as SND. Of these, 10 had adequate clinical records and had received L-DOPA, 4 of whom had a sustained response. Response to L-DOPA was defined as a definite motor response, i.e., improvement in bradykinesia, rigidity, tremor and/or gait, that lasted for at least 1 yr and continued to within 1 yr of death.

Ten control cases from the brain bank were matched for age: 7 of these died from myocardial infarction, 1 from a pulmonary embolus, 1 from aortic stenosis and cardiac failure and 1 from oesophageal carcinoma and bronchopneumonia.

Brains donated to the brain bank are cut midsagittally in half with one half immersion-fixed in 10% neutral formalin for 5 wks and the other frozen rapidly after death. Therefore, only half brains were available for histology, apart from Case 10, in which the whole brain had been fixed in formalin.

The striatum was examined using 7 μ m paraffin coronal sections taken from its anterior, mid and posterior parts. The anterior sections were taken at the level of the caudate head, the mid sections at the level of the anterior commissure and the posterior at the level of the mamillary bodies and thalamus. The mid striatal block was cut perpendicular to the medial surface of the hemisphere in a line passing immediately anterior to the anterior commissure and posterior to the optic chiasm. Sections were stained with haematoxylin and eosin (H and E), luxol fast blue and Nissl (LFB/N) and glial fibrillary acidic protein (GFAP), supplied by Dakopatts Ltd, using the peroxidase antiperoxidase method. Sections of the midstriatum were used for morphometry. The surface area of the putamen was measured using fine graph paper. Neurons were counted if they had a nucleolated nucleus and contained Nissl substance. Counts were made of the whole putamen and globus pallidus in one section at $\times 400$ magnification using an eyepiece graticule. For the caudate, 10 fields of 0.07 mm² evenly spread throughout the body of the caudate were counted and the sum total used. In the putamen, small neurons were counted separately from large neurons (diameter approximately double and Nissl substance more prominent and clumped).

For the substantia nigra, unilateral 7 μ m sections were taken in the transverse plane at the level where the third cranial nerve divides it from the ventral tegmental area (fig. 1A). The anatomy is relatively constant at this level and Hassler (1937) identified 14 groups of neurons in the pars compacta (fig. 1B). For the purposes of quantification these groups were simplified to 6 zones (fig. 1C). Sections were stained with H and E and these zones were delineated using a 0.13 mm Rotring pen under $40\times$ and $100\times$ magnification. The pars reticulata was marked off, but was not counted. Counts were performed at $400\times$ magnification. Thirty-six controls ranging in age from 21 to 91 yrs were used in order to calculate regression equations for age-related neuronal loss in total and regional counts ($P < 0.001\%$, except VI < 0.05 and VL $< 0.01\%$ in which the loss was less). Counts were then expressed as a percentage of the value derived from the corresponding regression equation.

The midpons, including the locus coeruleus, was examined from sections taken transverse to the long axis of the brainstem at the level of the superior margin of the middle cerebellar peduncle. For counts of the locus coeruleus, 7 μ m sections were stained with H and E and neurons counted at $\times 400$ magnification. For counts of the pontine nuclei, 14 μ m sections were stained with LFB/N and the neuronal count was taken as the average of 4 counts of nucleolated neurons within 4 fields of 0.07 mm² ($\times 500$ magnification).

The inferior olive was examined from a block taken of the upper medulla. Sections were cut at 14 μ m and stained with LFB/N. The neuronal count was taken from the average of 4 counts of nucleolated neurons in 4 fields of 0.1715 mm² ($\times 320$ magnification) from the 4 corners of the olive.

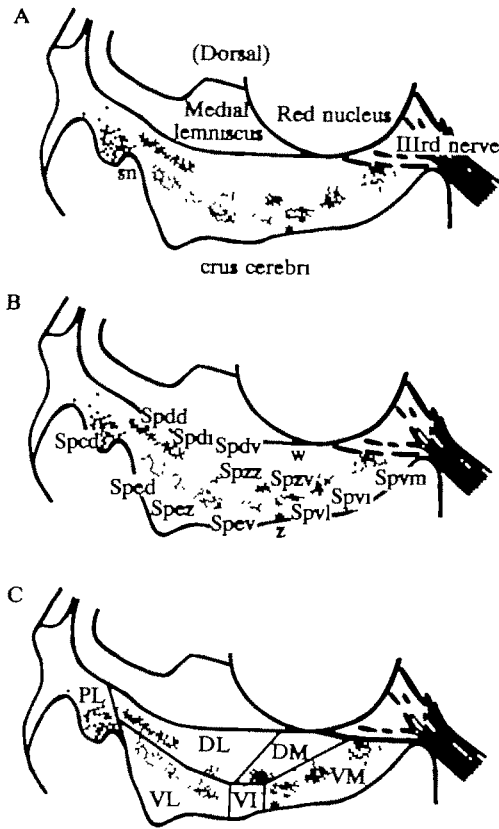


FIG. 1. Diagrammatic representation of the substantia nigra. A, anatomy. Each dot represents a pigmented neuron; sn = striatonigral fibres. B, Hassler's nomenclature. C, zones used for current study: ventromedial (VM); ventrointermediate (VI), ventrolateral (VL); dorsomedial (DM); dorsolateral (DL), pars lateralis (PL).

The cerebellum was examined from blocks of the hemisphere including the dentate nucleus. An average count of Purkinje cells was taken from 4 counts of 2 mm strips of cerebellar cortex.

Statistical methods. Significance was determined using Student's *t* test.

Cases responding to L-dopa

Case 1

A 67-yr-old female (duration of disease 3 yrs). Clinical diagnosis PD.

For 12 months, this patient experienced a disturbance of balance. She presented when she developed a right-sided tremor affecting the arm and leg followed by stiffness and slowness of walking. She was started on Sinemet 110 four times daily and had a moderate response. She began to fall frequently and 6 months later sustained an impacted fracture of the neck of her left femur. She then had urgency and occasional urinary incontinence. During her stay on the orthopaedic ward she snored loudly, keeping the other patients awake even after her bed was put in a side room with the door closed. Also, while on the ward she had a few episodes of urinary and faecal incontinence. She mobilized well and was stage IV on the scale of Hoehn and Yahr (1967) requiring a frame to walk. Over the next 6 months her condition deteriorated rapidly and she was incontinent at night. She was changed to Sinemet Plus (125) 1 tablet four times daily with no improvement. She was re-examined and found to have a resting tremor with marked bradykinesia and mild rigidity in all 4 limbs. Asymptomatic postural hypotension was found with a 50 mmHg fall in systolic blood pressure (diastolic static). Six months later, she was severely disabled (Hoehn and Yahr stage V) and was admitted to hospital. She was confined to bed and had developed pressure sores,

but was able to walk short distances with the aid of a frame and one nurse. She was severely dysarthric and complained of spasms in the throat. She also experienced dysphagia with reduced dietary intake and weight loss. The Sinemet Plus was increased to 8 tablets daily and there was end of dose worsening of her tremor. Addition of selegiline (Deprenyl) 5 mg daily and bromocriptine 5 mg three times daily had no beneficial effect. Three years from the onset, she died of bronchopneumonia.

Case 2

A 51-yr-old male (duration of disease 4 yrs). Clinical diagnosis MSA.

This patient presented with urinary urgency and impotence followed by loss of ejaculation and occasional dizziness on standing. Twelve months later, he developed unsteadiness of walking with dragging of the right leg and stiffness of the right hand with micrographia. Examination revealed an asymmetric bradykinetic-rigid syndrome with no tremor. He had poverty of facial expression, cogwheel rigidity of the right arm and lead pipe rigidity of both legs, right worse than left. He walked with a broad-based gait with no arm swing and loss of balance on turning quickly. There was equivocal cerebellar ataxia of the left arm, postural hypotension and left-sided pyramidal tract signs with hyperreflexia and an extensor plantar response. A diagnosis of MSA was made. He was started on Madopar 62.5 three times daily and the dose was gradually increased to Madopar 125 five times a day. He had a definite, but mild, response with on-off oscillations and drug-induced dyskinetic movements of the right arm. Near the end of a dose he would notice a worsening of his gait and if he was ever late taking a dose there would be a sudden deterioration, which was correctable when the Madopar was taken. Up until the time of his death he continued to have a response to L-dopa.

Case 3

A 78-yr-old male (duration of disease 8 yrs). Clinical diagnosis PD.

Disability started with a gradual onset of right-sided functional impairment with difficulty writing and walking. After 1 yr he was diagnosed as having PD and started on benzhexol with initial improvement. He then became depressed about declining sexual function and complained of a dry mouth. Within 2 yrs of the onset he was noted to have mild right-sided bradykinesia, cogwheeling on synkinesis and a disturbance of gait. He was started on Sinemet 110 with benefit and over the following years the dose was increased to 8 tablets daily. He was reassessed again 5 yrs later when he had facial immobility with infrequent eye blinking and drooling of saliva. He was dysarthric with a festinant speech. He had a flexed posture, shuffling gait and loss of right arm swing. There was generalized dyskinesia. He was given physiotherapy and changed to a regimen of Sinemet Plus 6 tablets daily and benzhexol 2 mg three times daily with improvement. By the eighth year of his illness, he was confused, paranoid and depressed with suicidal thoughts. He then began to fall frequently and to lose weight. He died in hospital with acute urinary retention and bronchopneumonia.

Case 4

A 72-yr-old female (duration of disease 5 yrs). Clinical diagnosis PD.

There was a gradual onset of slowness and stiffness of the left arm over 6 months in this patient. She was found to have a swollen and discoloured left hand and a diagnosis of Sudek's atrophy was made. Neck rigidity was noted and attributed to cervical spondylosis. After 1 yr, she was finding difficulty in walking and was falling. She had reduced facial expression, left arm rigidity and tremor of the left hand. She was started on Sinemet 110 2 tablets a day increasing to 6 and orphenadrine 50 mg three times daily. She had a good response with loss of demonstrable rigidity and no further falls. Despite treatment her disability progressed and after 4 yrs she began to fall again. By this time she was on Sinemet Plus 4 tablets daily and was experiencing L-dopa induced dyskinesia. It was still felt that she had a moderate response to L-dopa. She died of bronchopneumonia later that year.

Cases unresponsive to L-dopa

Case 5

A 56-yr-old female (duration of disease 5 yrs). Clinical diagnosis MSA.

This patient presented with gradual onset over 1 yr of difficulty dressing and washing due to slowness and difficulty initiating movement. She had slurred nasal speech with an expressionless face and generalized bradykinesia and rigidity. There was no tremor. She was started on Sinemet and had a mild unsustained

response. After 1 yr, she developed postural hypotension and increasingly troublesome urinary frequency with urgency. She was still mobile and able to rise from a chair unaided. After 5 yrs, however, she was profoundly bradykinetic and had developed an intention tremor. She also required urinary catheterization.

Case 6

A 59-yr-old female (duration of disease 10 yrs). Clinical diagnosis MSA.

This patient presented with dragging of the right foot and difficulty in writing. She was found to have right-sided rigidity and bradykinesia. She was started on Sinemet and apparently responded, but the drug was discontinued because of intolerable nausea. A year later, she was restarted on Sinemet and her walking improved. By the third year, her signs were still mainly right-sided, but she had developed postural hypotension. Left-sided disability appeared 5 yrs after the onset. A year later, she developed dystonic posturing of the neck and the foot. There was no significant response to bromocriptine 20 mg daily, which caused orofacial chorea, pergolide 3 mg daily, orphenadrine 150 mg daily or a single 1.2 mg dose of lisuride. A severe fixed torticollis with the head turned to the left appeared after 8 yrs. A diagnosis of MSA was made when she started to become incontinent of urine at night. There was no postural hypotension when she had been off treatment for several days, but her resting heart rate was 100/min with no variation on standing or deep breathing. Withdrawal of antiparkinsonian drugs did not lead to deterioration. She continued to get worse with the emergence of severe dysarthrophonia and died 10 yrs after the onset.

Case 7

A 61-yr-old female (duration of disease 10 yrs). Clinical diagnosis PD.

PD was diagnosed at the age of 52 yrs after this patient presented with a bradykinetic-rigid syndrome and she was started on L-dopa. Two yrs later, she was taking Sinemet 275 6 tablets daily and was experiencing visual hallucinations and hypotension. After 4 yrs treatment, she was admitted to assess her response to L-dopa, bromocriptine and benzhexol. Despite optimal doses of L-dopa there was no response and the other two drugs were of no benefit. She was then having syncopal episodes and had an intermittent resting tremor of both hands. In the sixth year, she developed dyskinesia on Sinemet 110 7 tablets daily, suggesting a therapeutic response. A year later, she was found to have a pseudobulbar palsy with emotional lability. After 9 yrs, she was severely bradykinetic, unable to walk and was profoundly hypophonic. There was no improvement by altering her L-dopa dose or adding selegilene. She died the following year.

Case 8

A 64-yr-old female (duration of disease 8 yrs). Clinical diagnosis MSA.

This patient presented with gradual onset over 3 yrs of difficulty in writing followed in the fourth year by a tremor of the right hand, difficulty in walking, falling and slurring of speech. A diagnosis of Parkinson's disease was made and she was started on Sinemet, which made her feel more unsteady. In the sixth year of her illness, she had a further trial of Sinemet 110 three times daily, which did not result in any improvement. She was investigated for faecal incontinence by a surgeon. A year later, she was noted to have a flexed posture, intermittent resting tremor of the right hand, minimal bradykinesia and rigidity of the right arm and leg. Autonomic function testing was abnormal with some impairment of vagal reflexes. Increasing her Sinemet to 275 four times daily failed to improve her condition. At this point, she was thought to have MSA. In the eighth year, she had deteriorated to such a degree that she was confined to bed and she died later that year.

Case 9

A 62-yr-old male (duration of disease 6 yrs). Clinical diagnosis MSA.

This man presented with gradual onset of difficulty in rising from a chair, turning over in bed at night, unsteadiness and a deterioration in his handwriting. He also complained that his voice had changed. In the second year, he was diagnosed as PD and was started on benzhexol with a good but short-lived response. His condition deteriorated rapidly and Sinemet and later selegilene were added, but without benefit. He complained of sexual difficulties and developed hesitancy of micturition for which a transurethral prostatectomy was performed. The following year, he developed a focal dystonia of the neck with antelexion and slight turning to the left. Because of continued hesitancy and one episode of retention he had a cystoscopy. His prostate was normal and the bladder poorly trabeculated suggesting a nonobstructive cause. After 5 yrs of illness he was noted to have a severe bradykinetic-rigid syndrome with a resting tremor and postural

hypotension with impairment of sympathetic vasoconstriction on autonomic testing. He also had pyramidal signs with mild weakness of all 4 limbs, hyperreflexia and bilateral extensor plantar responses. There was early impairment of vertical eye movements on neuro-otological testing and marked antelexion of the neck. He was diagnosed as MSA. During the final year his mobility worsened and he died after repeated chest infections.

Case 10

A 68-yr-old male (duration of disease 2 yrs). Clinical diagnosis PD.

The patient presented with a 1 yr history of falling, difficulty in walking, difficulty manipulating objects and a soft slurred speech. On examination, he was bradykinetic with a flexed posture, festinant gait without arm swing, mask-like facies and cogwheel rigidity of all 4 limbs. There was no tremor. His speech was monotonous, he had profuse dribbling of saliva and his writing was slow, small and cramped. He was started on Sinemet 110 3 times daily and benzhexol 2 mg 3 times daily, but failed to respond. One month later he collapsed while urinating. Re-examination at this time revealed marked axial rigidity. Six months later, he was admitted because of a severe and relentless deterioration in mobility. Selegiline 10 mg daily was added and the Sinemet 110 increased to 5 tablets daily, but there was no improvement and he continued to deteriorate with frequent falls. In the final month of life he required an indwelling urinary catheter for retention. He died of bronchopneumonia after a fall.

RESULTS

Clinical findings

The age of onset and duration of disease was approximately the same for the L-dopa responsive and nonresponsive groups. Age of onset ranged from 47 to 70 (mean 62) yrs in the responders and 49 to 66 (mean 56) yrs in the nonresponders with no significant difference. Duration of disease ranged from 3 to 8 (mean 5) yrs in the responders and 2 to 10 (mean 7) yrs in the nonresponders again with no significant difference.

The parkinsonian features for the 10 cases under study compared with 39 cases of PD in the brain bank were as follows. Resting tremor as the initial symptom was present in only 1/10 compared to 73% of PD. Later in the illness, a further 4/10 developed resting tremor. A symmetric onset was not diagnostically helpful, because in 6/10 the onset was definitely asymmetric compared with 88% in PD. Early falling, atypical for PD, was present in 3 cases. Severe dysphonia and dysphagia occurred in 2 cases and in 1 this was accompanied by excessive snoring suggestive of velopharyngolaryngeal paralysis. Torticollis was present in 1 case, antecollis in 1 and axial rigidity in 2.

Response to L-dopa was clearly different between the responder and nonresponder groups using the study's definition. Response was defined as a substantial improvement present for at least 1 yr and sustained to within 1 yr of death. The presence of L-dopa dyskinesia was not used in the responder group as unequivocal evidence of response. In the responder group, the response duration ranged from 2 to 7 (mean 4) yrs and the period before death where the patient had lost response ranged from 0 to 1 (mean 0.5) yr. In the nonresponsive group, 3 out of 6 patients responded to a slight degree for 1 to 4 (mean 2.3) yrs and the period of lost response before death was 3 to 7 (mean 5) yrs. The figures for the responders if anything are underestimated and those of the nonresponders overestimated.

Cerebellar signs were detected in 2 cases with a broad-based gait in 1 and an intention tremor in the other. Autonomic disturbance was present in 7 cases and in the 3 remaining cases there were features in the histories which might suggest involvement. Pyramidal

signs were present in 2 cases. None of the cases had a family history of neurological disease.

Correct diagnosis in the responder group was made in 1/4 and in the correctly diagnosed case, which presented with autonomic failure, diagnosis was made at the time when the extrapyramidal features appeared, 1 yr after onset. In the nonresponder group, 4/6 were correctly diagnosed after a disease duration ranging from 2 to 8 (mean 5) yrs or time undiagnosed as a percentage of disease duration: 40 to 88% (mean 72%).

In the cases incorrectly diagnosed, all 5 had possibly atypical features for PD either in their initial symptoms, with no resting tremor in 4 and early falling in 3; or later, with the development of autonomic features in 3, absence of response to L-dopa in 2 and severe dysphonia/dysphagia in 2 with probable velopharyngolaryngeal paralysis in 1.

Pathological findings

Unfixed brain weights were within the normal range for age (Dekaban and Sadowsky, 1978) except for Case 8 which weighed 1095 g (normal: mean 1240, SD 20). The results of morphometry are shown in Table 1.

Striatum

Macroscopically, the putamen was pigmented and shrunken in the 6 nonresponders. However, in the responder group, 2 cases appeared normal and in the other 2 there was only minor pigmentation in the dorsal putamen without obvious shrinkage.

TABLE 1. GENERAL MORPHOMETRY

Case	1	2	3	4	5	6	7	8	9	10L R
Caudate	116	99	110	121	28	76	32	77	85	71 60
Putamen (small)	3344	3476	6637	6420	120	576	68	767	816	340 278
Putamen (large)	39	49	35	96	3	7	6	28	1	1 1
Putamen SA (mm ²)	92	72	91	94	45	36	50	48	40	53 45
Globus pallidus	318	273	161	383	53	20	104	160	134	223 232
Substantia nigra	138	76	174	189	18	26	20	105	88	36 182
Locus coeruleus	28	7	62	25	1	5	7	*	12	13 30
Pontine nuclei	8	2	26	22	6	8	6	9	15	22
white matter**	+	+++	—	—	++	+	++	++	+	—
Inferior olive	5	4	22	21	5	9	9	8	*	*
Cerebellum										
Purkinje cells	9	5	14	14	8	9	10	*	9	14
White matter	++	+++	—	—	++	++	++	*	++	—

SA = surface area (Controls: mean 127 mm²; range 100–154 mm²). White matter pallor — = absent; + = mild; ++ = moderate; +++ = severe * Not available ** Transverse pontine fibres.

Neuronal counts of 10 aged-matched controls (mean, range): caudate (152, 138–162), putamen: small cells (11037, 8567–14886), large cells (117, 64–173); globus pallidus (390, 321–448); substantia nigra (637, 417–873); locus coeruleus (82, 71–94); pontine nuclei >20; inferior olive > 20; cerebellar cortex >13

Measuring the surface area of the midputamen revealed a significant difference between controls:responders ($P < 0.02$) and responders:nonresponders ($P < 0.001$). The ranges were as follows: controls 100–154 (mean 127) mm²; responders 72–94 (mean 87) mm²; nonresponders 36–53 (mean 45) mm².

When the SND cases and controls were taken as a whole there was a good correlation between the surface area and the neuronal count ($r = 0.924$, $P < 0.001\%$) with a regression equation: neuronal count = $118 \times \text{surface area} - 4535$. However, for individual cases the neuronal count could not be reliably estimated from the surface area.

Microscopically, there was variable astrogliosis, neuronal loss and pigmentation in the astrocytes and few remaining large neurons (figs 2, 3). We did not find any sparing of the large neurons. The ratio of small neurons to large ranged in the Control group from 63 to 198:1 (mean 104) and in the SND cases from 11 to 816:1 (mean 170) with no significant difference between the two groups.

Diagnosis was difficult in Case 4, because the putamen appeared normal on H and E and LFB/N stains and a phosphotungstic acid haematoxylin (PTAH) stain was inconclusive. PD was suspected, but no Lewy bodies were found despite nigral cell loss. Putaminal gliosis and neuronal loss was only appreciated when a GFAP stain and neuronal count were performed.

In order to gain some idea of the distribution of the disease in the striatum the astrogliosis was drawn out for each case (*see* fig. 4). As can be seen, it appears to start dorsally in the posterior two-thirds and as it progresses spreads ventrally and anteriorly in a dorsolateral fashion. Also, the astrocytes in the dorsal putamen tended to be more hypertrophic than the ventral. The body of the caudate nucleus showed

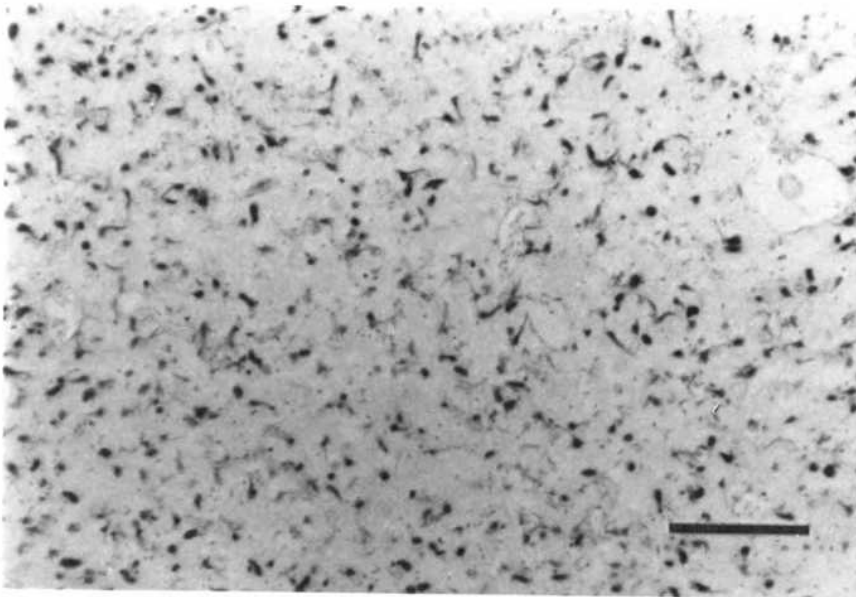


FIG. 2. Putaminal gliosis. Abundant fibrillary astrogliosis in Case 10. GFAP, $\times 90$. Bar = 200 μ m.

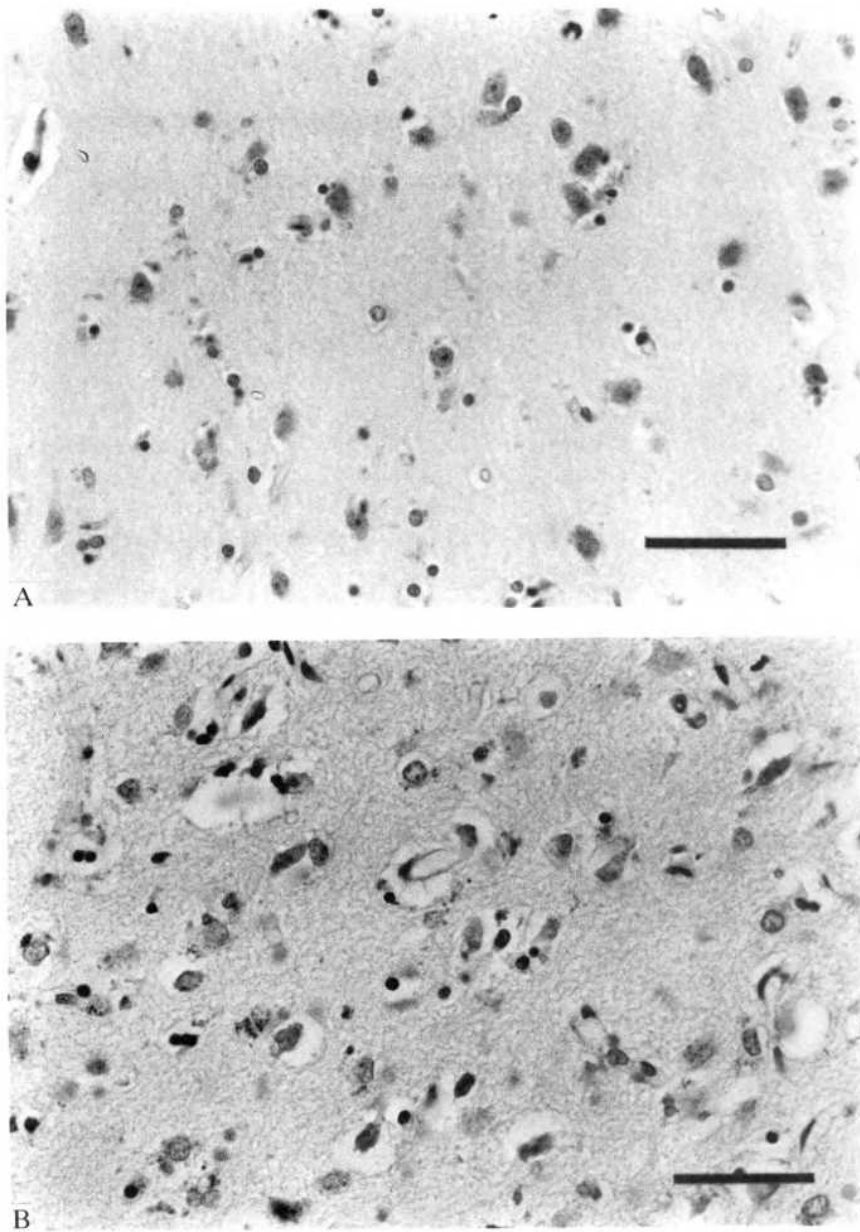


FIG. 3. Putaminal neuronal depletion. A, normal putamen showing numerous nucleolated small neurons. B, SND putamen (*Case 8*) with multiple astrocytes, intracellular pigmentation and no identifiable neurons in this field. Nissl. Bars = 50 μ m.

macroscopic atrophy in 4 out of 10 cases and there was no visible pigmentation in any case. Microscopically, all cases showed gliosis, neuronal loss and variable pigmentation although in the milder cases this was only apparent on GFAP stains and neuronal counting.

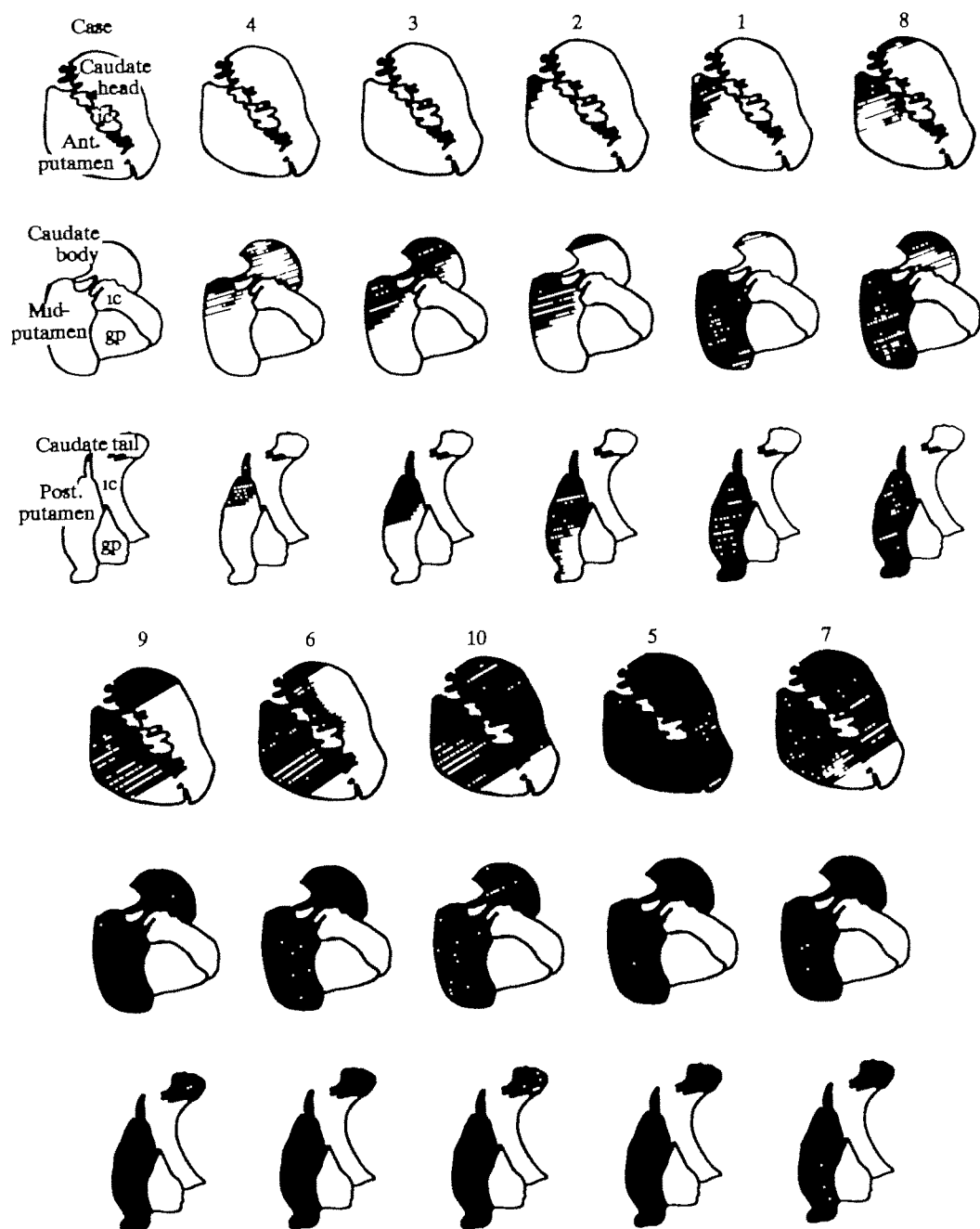


FIG. 4. Topography of striatal involvement (atrophy is not represented) at 3 coronal levels: anterior, mid, and posterior. Cross-hatching indicates area of macroscopic changes and single hatching area of macroscopic gliosis. Cases arranged from left to right in order of decreasing putaminal neuronal count at midlevel (except Cases 4 and 9 which were switched with Cases 3 and 8, respectively, and which had approximately equivalent counts). ic = internal capsule, gp = globus pallidus.

Changes were maximal in the body of the caudate dorsally and with increasing severity extended ventrally and anteriorly/posteriorly into the head and tail. Dorsally, the caudate lesion was continuous with the putaminal lesion through the striatal bridges traversing the internal capsule.

Globus pallidus

Macroscopic atrophy of the globus pallidus was evident in 2 cases. Microscopically, however, all cases showed gliosis on GFAP staining. In 3 cases, this was most marked in the external segment while in the other cases it was more evenly distributed throughout the two segments. There was variable loss of myelinated fibres on the LFB/N stain. The neuronal counts ranged from being normal in 1 responder to markedly reduced.

Substantia nigra and locus coeruleus

Macroscopically, the substantia nigra and locus coeruleus showed variable pallor. Microscopically, there was neuronal loss, with gliosis and free pigment. There were no Lewy bodies.

There is neuronal loss with ageing in the substantia nigra (McGeer *et al.*, 1977) so regional and total counts were expressed as a percentage of normal counts derived from regression equations of 36 controls. The results are shown in Table 2. When cases were taken as a whole the degree of regional involvement, in decreasing order, was as follows: (1) VL; (2) VI; (3) PL; (4) DL; (5) VM; (6) DM (*see* fig. 5). Most surprising was the marked asymmetry of Case 10 in which both halves of the brainstem were available. There was roughly a 5-fold difference in the neuronal counts between the two sides. This difference, but to a lesser extent, was also seen in the locus coeruleus.

Olivae, pons and cerebellum

Seven out of the 10 cases had involvement of the olivopontocerebellar system. In the 2 cases that had cerebellar signs, the Purkinje cell counts were the lowest.

TABLE 2 SUBSTANTIA NIGRA REGIONAL COUNTS*

Case	Region**						Total
	VM	VI	VL	DM	DL	PL	
1	46	13	6.0	44	30	26	25
2	16	2.5	1.1	30	20	20	12
3	56	5.4	2.2	60	68	63	33
4	61	45	7.8	70	41	31	35
5	6.4	0	0	6.3	3.5	2.9	3.0
6	9.2	0	0	8.0	7.3	4.4	4.4
7	2.0	0	0	12	10.3	6.1	3.6
8	39	13	1.6	29	19	22	18
9	32	10	0	43	9	6.1	15
10 L	10	0	0	18	18	4.9	6.4
10 R	48	26	23	44	33	34	33

* Age-adjusted counts, expressed as a percentage of normal. ** See fig. 1 for explanation of regions.

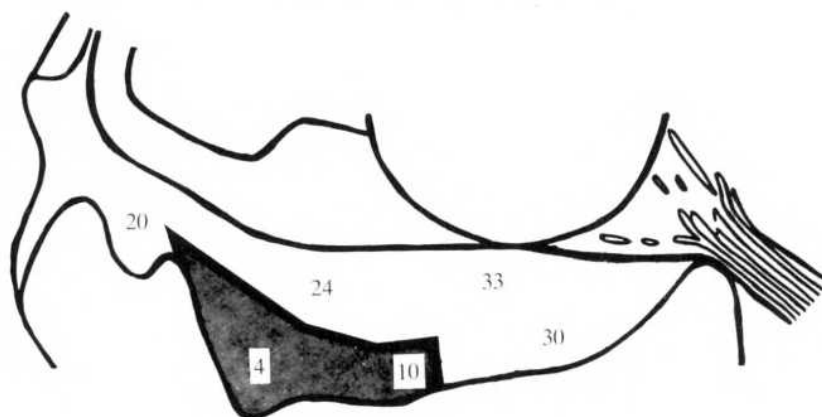


FIG. 5. Substantia nigra regional counts in SND. Mean of age-adjusted counts expressed as percentage of normal. Most severely affected areas shaded.

Correlation between nuclei

Within the striatum, the caudate counts correlated well with the putaminal counts ($r = 0.817$, $P < 0.01$). The method of counting was different for these two areas and to look at the relationship in greater detail the putaminal and caudate counts were expressed as a percentage of the mean control count. Correlation was maintained ($r = 0.91$, $P < 0.001$) and the regression equation was: caudate % = 0.74 (putamen %) + 38% . There was no significant correlation between the globus pallidus count and the putaminal count, but some correlation with the caudate ($r = 0.69$, $P < 0.02$).

The substantia nigra total counts correlated best with the putamen and the locus coeruleus and to a lesser extent the caudate and globus pallidus (see Table 3). Correlation was increased when looking at individual nigral regions. For the putamen and locus coeruleus, correlation was good for all regions except for VI and VL, in which the neuronal loss was most severe. The caudate and globus pallidus counts correlated best with the medial nigra. The locus coeruleus counts did not correlate with either the caudate or the globus pallidus and there was only very weak correlation with the putamen ($P < 0.05$).

TABLE 3. NEURONAL COUNT CORRELATION BETWEEN SUBSTANTIA NIGRA AND OTHER NUCLEI*

Region**	Caudate		Putamen		Pallidum		Locus coeruleus	
VM	0.02	(0.713)	0.02	(0.693)	0.05	(0.625)	0.001	(0.805)
VI	n.s.	(0.470)	n.s.	(0.468)	0.02	(0.695)	n.s.	(0.333)
VL	n.s.	(0.084)	n.s.	(0.055)	n.s.	(0.435)	n.s.	(0.367)
DM	0.01	(0.778)	0.001	(0.801)	0.02	(0.714)	0.01	(0.753)
DL	0.05	(0.640)	0.001	(0.916)	n.s.	(0.500)	0.001	(0.960)
PL	n.s.	(0.586)	0.001	(0.765)	n.s.	(0.425)	0.001	(0.950)
Total	0.05	(0.661)	0.02	(0.694)	0.05	(0.663)	0.001	(0.817)

* Unbracketed values are confidence limits and those in brackets the correlation coefficients. ** See fig. 1 for explanation of regions. n.s. = not significant.

L-dopa response

The putaminal counts were significantly greater in those cases that responded to L-dopa than those that did not ($P < 0.001$). However, the nigral counts were also higher in the responders, but not nearly to the same level of significance ($P < 0.05$). Additional evidence that the putamen was more relevant than the nigra in determining response came from Case 10. The nigral lesions were grossly asymmetric, but the clinical features as well as the putaminal lesion were symmetric.

DISCUSSION

Clinical aspects

SND is notoriously difficult to differentiate from PD (Adams *et al.*, 1964) and in our series only half of the 10 cases were correctly diagnosed. However, in all the cases there were additional features, which were suspicious of SND.

The age of onset was not a useful differentiating factor. Review of 32 cases in the literature with a primary diagnosis of SND showed an average age of onset in SND of 54.8 (range 39–73) yrs, which is comparable with 55.3 yrs in PD (Hoehn and Yahr, 1967). Our datum was also in agreement with an average age of onset of 54.8 ± 8.6 yrs.

Progression is far more rapid in SND than in PD. The mean duration of disease to death in PD is 14 yrs (Stern, 1987). This is significantly different ($P < 0.001$) from our group with an average duration of 6 (range 2–10) yrs. This is consistent with the literature (average 5, range 0.5–15, yrs). We found that response to L-DOPA did not significantly alter the duration of disease.

The onset of parkinsonism in SND may differ from PD with resting tremor being less frequent and in our cases only 1 presented with tremor. It has also been claimed that the onset is more often symmetric, but review of the literature shows that up to 50% of cases begin asymmetrically. In our series only 40% may have had a symmetric onset compared with 12% of PD cases collected over the same period of time.

We found that falling early in the disease was an important clue, occurring in 3/10 cases. This has been previously reported in 1 case by Andrews *et al.* (1970). Early lenticular involvement in SND probably affects the integrity of postural reflexes leading to falls. Lacunar infarction and haemorrhage of the lenticular nucleus is known to cause sudden falling and severe postural instability (Labadie *et al.*, 1989).

Two of our cases were marked by severe dysphonia/dysphagia, which has been found to be a helpful pointer (Rajput *et al.*, 1972; Takei and Mirra, 1973; Boudin *et al.*, 1976). In 1 of our cases, this was accompanied by excessive snoring, presumably due to the palatal component of a velopharyngolaryngeal palsy. Williams *et al.* (1979), in a study of 12 patients with MSA, found evidence in two-thirds of moderate to severe laryngeal abductor paralysis. The initial symptom was snoring followed by inspiratory/expiratory stridor and occasional sleep apnoea. There was no relation to the stage of the disease or the degree of dysarthria. The posterior cricoarytenoid muscles appear atrophic and it has been postulated that it is due to involvement of the nucleus ambiguus, but this has not been proven (Bannister *et al.*, 1981).

Associated neurological signs are more common in SND than PD, but none of these is in anyway pathognomonic. Clinical diagnosis of SND in our series was principally based on the presence of autonomic features. However, autonomic failure can occur

in PD and is indistinguishable from that seen in SND (Fichefet *et al.*, 1965; Graham and Oppenheimer, 1969). Also, autonomic-like symptoms are relatively common in PD and their significance is difficult to assess (Quinn, 1989). Cerebellar signs if and when present may be masked by the parkinsonism and only 2 of our 10 cases had signs. A positive Babinski response can be seen in young onset PD and diagnostic confusion may also occur with the striatal 'dystonic foot' (Duvoisin *et al.*, 1972). In the older age group, signs such as amyotrophy of the hand and pyramidal signs in the leg may result from concomitant cervical spondylosis and urinary symptoms from benign prostatic hypertrophy.

One of the most important pointers to the diagnosis is failure to respond to therapeutic doses of L-dopa (Izumi *et al.*, 1971). This is probably due to superadded striatal involvement and loss of postsynaptic dopamine receptors. There has been only one case of pathologically proven SND (Fève *et al.*, 1977) and several putative cases (Lees, 1988) that have derived sustained benefit from L-dopa. It could be postulated that these cases might have less severe striatal cell damage. We focused our attention on the putamen, because it is believed that function of this structure is predominantly motor while that of the caudate is more concerned with cognition (De Long *et al.*, 1983). We found that the response to L-dopa was related to preservation of the putamen as suspected. In the case that did respond and in which a diagnosis was correctly made, the degree of response was felt to be less than that of typical PD. Subcutaneous apomorphine and oral L-dopa tests may be helpful in distinguishing those cases that will respond to chronic treatment, but will not distinguish SND from PD conclusively except that a negative response would be strongly against PD (Barker *et al.*, 1989).

Neuroimaging offers promise in refining the clinical diagnosis of the parkinsonian syndrome, but it is yet to be determined how sensitive these investigations are and a correlative clinicopathological study is needed. CT scanning may detect cerebellar atrophy if there is a significant OPCA component. MRI can show putaminal involvement with atrophy on T1 inversion recovery images and reduced signal on T2-weighted sequences particularly in a posterior and lateral distribution (Pastakia *et al.*, 1986). It has also been shown that the degree of signal fallout correlates with the degree of rigidity (Brown *et al.*, 1987). PET scanning using fluorodopa uptake shows a more severe caudate abnormality than is seen in PD (Brooks *et al.*, 1990) presumably reflecting more extensive involvement of the substantia nigra.

To conclude, in our incorrectly diagnosed cases, features retrospectively suggestive of the diagnosis were the absence of tremor as a presenting complaint, the early appearance of autonomic symptoms, absence of response to L-dopa, falls early on in the illness and excessive snoring. In none of the cases was neuroimaging used to make a diagnosis. The repercussions were the continuation of unnecessary drug therapy with inappropriate investigation and treatment of associated autonomic features in some cases. However, inability to diagnose SND need not jeopardize management of the patient if a symptomatic approach is taken.

Pathological aspects

Macroscopically, in the putamen, the most striking features are atrophy and tannish discolouration and in severe cases a cribriform appearance. In 4 cases, atrophy was only detected on measurement of the surface area and in 2 there was no visible

pigmentation. Therefore, SND cannot be excluded on naked eye appearances. We found a good correlation between the surface area and the neuronal count of the putamen. However, for the individual case, surface area was not reliable in obviating the need to perform the more time consuming count. In 4 out of 10 cases, the caudate appeared shrunken without discolouration and the remaining cases appeared normal. Although the striatal lesion is often considered to be bilaterally symmetric, in 3 of 4 original cases of Adams *et al.* (1961) the lesion was asymmetric. Unfortunately, because we used half brains we were unable to examine this point.

Microscopically, there was intracellular pigmentation, neuronal loss, gliosis and loss of myelinated fibres. However, in mild cases, diagnosis was difficult and we found it necessary to examine a GFAP stain to find gliosis and only with quantification was it possible to appreciate neuronal loss. In past studies, immunostaining was not available and morphometry was not performed. This may explain why the caudate has been deemed to be normal in several reported cases (Adams *et al.*, 1964; Mayo and Barron, 1966; Jellinger and Danielczyk, 1968; Borit *et al.*, 1975; Buonanno *et al.*, 1975). In all our cases, the caudate was involved and neuronal loss correlated well with that of the putamen ($P < 0.01$). Some authors have suggested sparing of large neurons (Adams *et al.*, 1961; Takei and Mirra, 1973; Vuia, 1975), but these were qualitative assessments and we found no sparing quantitatively.

In SND there is a predilection for the posterior two-thirds of the putamen (Adams *et al.*, 1964; Takei and Mirra, 1973; Borit *et al.*, 1975; Feve *et al.*, 1977). There is also a dorsolateral predilection: Adams *et al.* (1964) found a dorsolateral predilection in 1 case; Sharpe *et al.* (1973) found that the dorsal two-thirds were more involved in 1 case and Takei and Mirra (1973) found in the less affected anterior two-thirds that there was a dorsolateral distribution. In our series, by studying several cases of varying severity we were able to document the spread of disease. In the mildest cases the disease was confined to the dorsal part of the posterior two-thirds and with increasing severity this spread ventrally and anteriorly, in a dorsolateral manner (fig. 2). The caudate also had a regional distribution, the changes appearing to start in the dorsal part of the body spreading both anteriorly, posteriorly and ventrally.

The reason for this distribution in SND is unknown, but there is an intriguing anatomical similarity between the distribution of the striatal and the nigral lesions. The nigral projections to the dorsal putamen arise diffusely, but there is a preponderance from the lateral and caudal parts in the monkey (Szabo, 1980), corresponding to the ventrolateral zone (VL) of our study. We found this zone to be the most heavily involved in SND. A possible explanation for this anatomical congruity could be transsynaptic degeneration. However, this does not seem likely on two counts. First, we found no correlation between the neuronal counts of the putamen and VL, VL being severely depleted of cells irrespective of the degree of putaminal loss. Although VL neuronal counts were low we considered that more extensive counting was unlikely to reveal a relationship. Secondly in PD, VL is also more severely affected than other zones in the nigra (Hassler, 1938). Correspondingly, there is a regional loss of striatal dopamine maximal in the dorsal posterior two-thirds of the putamen and the dorsal caudate anteriorly (Kish *et al.*, 1988), lending corroborative evidence of the projection of the nigral lesion. However, despite some evidence of transsynaptic degeneration with atrophy of medium sized spiny neurons, which receive the nigral projection (McNeill *et al.*, 1988) and a

suggestion of quantifiable neuronal loss (Bernheimer *et al.*, 1973; Bugiani *et al.*, 1980), the putamen is essentially intact (Hassler, 1938). Therefore, although the lesion in VL is similar for PD and SND, the putaminal lesion is very different. Alternatively, there was good correlation between the counts of the putamen and other parts of the nigra: dorsolateral (DL) and medial (DM, VM). A possible link in the latter could be the suggestion that striatal striosomes may project directly to the medial substantia nigra pars compacta (Graybiel, 1989). In conclusion, there appears to be an anatomical relationship between the lesions of the substantia nigra and the striatum, but there is no convincing evidence for conventional transynaptic degeneration.

The distribution of the putaminal lesion of Huntington's disease is similar to SND. Neuronal loss is greatest in the posterior and middle parts (Dunlap, 1927) with a predilection for the dorsal region (Schröder, 1931). In the cases with minimal pathology reported by Vonsattel *et al.* (1985), there was mild gliosis of the putamen in a posterolateral distribution.

The reason for a localization of pathology to the dorsal putamen in different diseases is uncertain. Motor cortex input to the striatum has a somatotopic distribution. Although there is overlap and variability in primates, the leg area projects mainly to the dorsal putamen, the face area to the ventral putamen and the arm area to the region in between (Künzle, 1975). Immunohistochemically there are differences, the dorsal compared with the ventral putamen having a reduced density of neurons containing nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d), somatostatin and neuropeptide Y (Ferrante *et al.*, 1987).

In the globus pallidus there is loss of myelinated fibres, gliosis and variable loss of neurons (Adams *et al.*, 1964). There is also pallor of the pallidal fibres to the thalamus, ansa lenticularis and lenticular fascicularis (Adams *et al.*, 1964; Takei and Mirra, 1973). Takei and Mirra (1973) found neuronal preservation in 5 out of 7 cases. Many authors have noted exclusive involvement of the external segment (Adams *et al.*, 1964; Mayo and Barron, 1966; Jellinger and Danielczyk, 1968; Sharpe *et al.*, 1973; Takei and Mirra, 1973; Buonanno *et al.*, 1975; Feve *et al.*, 1977). In our study, 3 out of 10 cases had involvement predominantly of the external segment and in the other 7 cases both segments were involved. In all but 2 cases there was significant neuronal loss, both cases coming from the L-dopa responsive group, in which the disease was generally milder. It has been suggested that the putaminal lesion is responsible for the loss of myelinated fibres, which arise or pass through this area, and that the neuronal loss is secondary to transynaptic degeneration (Adams *et al.*, 1964; Jellinger and Danielczyk, 1968). We were not able to support the latter hypothesis, only finding weak correlation between counts of the globus pallidus and the caudate ($P < 0.02$).

The substantia nigra and locus coeruleus are pigmented nuclei and in SND they are macroscopically pale. Microscopically, there is neuronal loss, gliosis and free pigment. In our series, the degree of quantifiable neuronal loss varied from mild to extreme. Regionally, the order of involvement is shown in fig. 5 with loss greatest in the ventrolateral zone (VL). We found a good correlation between the counts of the substantia nigra and the locus coeruleus with a pattern of correlation dissimilar from that of the striatum suggesting a different relationship possibly based on pigmentation or cell size. Of interest was the marked degree of asymmetry of the nigral and locus coeruleus lesions in Case 10, reinforcing the idea that this disease need not be symmetric.

Lewy bodies are a necessary finding in PD, but in SND they only occur in 3.8–7.5% of reported cases (Gibb, 1987). As has been discussed, there may be difficulty in recognizing the striatal lesion in some cases of SND and if there are incidental Lewy bodies (Forno, 1969), especially in the elderly, an erroneous diagnosis of PD may be made. Therefore, the incidence of Lewy bodies in SND might be higher. Alternatively, it may be that the Lewy bodies seen in a small number of cases of SND represent a coincidentally distinct pathological process (i.e., PD). We feel that in every case of Parkinson's syndrome, the putamen should be examined carefully regardless of whether Lewy bodies are present or not.

Involvement of the olivopontocerebellar system is characterized by neuronal loss in the pontine nuclei, inferior olives and the cerebellar Purkinje cells, together with pallor of the pontine transverse fibres/middle cerebellar peduncles, the hila of the inferior olives and cerebellar white matter. In our series, the majority (7/10) of cases had quantifiable neuronal loss. However, cerebellar signs were only found in the 2 cases with the most severe involvement. This suggests that lesion of this system is frequent in SND.

Taking the other perspective, Berciano (1982) reviewed 63 cases of sporadic OPCA (SOPCA) and 54 cases of familial OPCA (FOPCA) in the literature. He found the percentage of SOPCA/FOPCA cases with pathology in the striatum was 38/22%, in the substantia nigra 48/46% and in the locus coeruleus 22/15%, respectively. Initial clinical presentation was cerebellar in 90% and parkinsonian in 11%, rising as the disease progressed to 55/39% (SOPCA/FOPCA).

Conclusions

Striatonigral degeneration is a relatively common cause of patients presenting with a parkinsonian syndrome. However, it is frequently impossible to distinguish it in life from Parkinson's disease, especially when there is a therapeutic response to L-dopa. In the future, however, neuroimaging techniques may be able to demonstrate striatal pathology reliably and thereby provide a pointer to the diagnosis. It may also become possible to detect the subclinical olivopontocerebellar lesions providing a highly suggestive distribution of nuclear cell loss. The similar distribution of putaminal cell loss in striatonigral degeneration and Huntington's disease is intriguing. Immunohistochemical analysis of striatal architecture (Graybiel, 1989) may help to explain why the two disorders present with a different movement disorder. Relative preservation of the nigra in Huntington's disease may be important. The frequency of striatonigral degeneration presents problems in the selection of patients for clinical trials in Parkinson's disease. Failure to respond to oral L-dopa or subcutaneous apomorphine, falls or significant autonomic dysfunction in the first year of illness should probably be regarded as exclusion factors.

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CORTICAL OUTFLOW TO PROXIMAL ARM MUSCLES IN MAN

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SUMMARY

Corticospinal influences on two antagonistic muscles of the shoulder were studied in 6 normal volunteers. Recordings were made of the discharges of single motor units from the deltoid and pectoralis major muscles and poststimulus time histograms constructed following either anodal electrical or magnetic cortical stimulation via the scalp. Contralateral anodal stimulation caused narrow short-latency peaks of excitation in motor units from both muscles, probably indicative of the arrival of the D or direct corticospinal volley. The size of the peaks led to estimates of the underlying excitatory postsynaptic potentials (EPSP) amplitude of 5.5 mV for the deltoid and 2.2 mV for the pectoralis motor units. Magnetic stimulation over the vertex caused multiple early peaks of excitation in motor units from both muscles but these peaks began at a greater latency than those produced by anodal stimulation. Additionally, magnetic cortical stimulation (and, occasionally, contralateral anodal stimulation) caused a previously undescribed period of medium latency excitation in both muscles. These medium latency periods of excitation differed from the earlier events in that they occurred independently of the direction of current flow in the magnetic coil. This raises the possibility that they are the consequence of stimulation of bilaterally distributed cortical motor outflow pathways. The short-latency excitation strongly suggests that, in man, corticomotoneuronal projections exist to proximal as well as distal muscles of the contralateral arm. The strength of the projection to deltoid assessed by this method is similar to that to an intrinsic muscle of the hand and significantly larger than that to its antagonist, pectoralis. The possible bilateral organization of the additional medium-latency projection to these proximal arm muscles may contribute to two characteristic clinical features after a unilateral cerebral lesion, such as stroke: the relative sparing of proximal arm strength compared with distal and, secondly, ipsilateral weakness.

INTRODUCTION

The neurological syndromes that result from discharging or destructive lesions of the brain have unequal effects on different muscle groups. In the arm, distal muscles are usually the first to be involved by epileptiform activity (Jackson, 1873) and are more severely affected by stroke than proximal muscles (e.g., Gowers, 1893; Colebatch and Gandevia, 1989). These clinical observations are commonly believed to be due to the characteristics of the corticospinal projection to different muscles. Experimental studies on monkeys have shown that the monosynaptic projection to spinal motoneurons is more powerful for distal muscles of the arm; thus degenerating terminals are most numerous around motoneurons innervating distal muscles (Kuypers, 1981) and stimulation of the cortex produces the largest compound EPSPs (excitatory postsynaptic potentials) in

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motoneurons innervating intrinsic hand muscles (Phillips and Porter, 1964; Clough *et al.*, 1968). An alternative, possibly related, basis for the clinical finding of relative sparing of proximal arm muscles is the presence of bilateral innervation (Colebatch and Gandevia, 1989; Jones *et al.*, 1989). In monkeys, there is evidence of such bilaterally distributed pathways relaying in the brainstem (Brinkman and Kuypers, 1973); in man the bilateral influences of the motor cortex have traditionally been attributed to the anterior corticospinal tract, although the evidence to support this is scant (Weil and Lassek, 1929; Schoen, 1964).

The development of noninvasive methods of cortical stimulation (Merton and Morton, 1980; Barker *et al.*, 1985) has provided a method of directly examining the properties of the corticospinal outflow in man. Histological evidence indicates a substantial increase in the size of the pyramidal tract in man (Lassek, 1954) as well as a much more extensive corticomotoneuronal projection (Kuypers, 1981). Supporting these conclusions, stimulation of the motor cortex in man has caused short-latency, probably monosynaptic, activation of nearly every muscle studied, not only including those of the limbs but also muscles as diverse as the lumbar paraspinals (unpublished observations) and the anal sphincter (Merton *et al.*, 1982). These findings indicate that the properties of the corticospinal tract in man may differ importantly from those in lower primates.

The aim of the present study was to examine in detail the nature of the cortical projection to 2 proximal muscles of the arm, the deltoid and the pectoralis major, and to compare these findings with published results for an intrinsic hand muscle, the first dorsal interosseous. Single motor units were isolated and poststimulus time histograms collected to allow a quantitative estimate to be made of the underlying EPSP (Ashby and Zilm, 1982; Fetz and Gustafsson, 1983). We found that both muscles have a probable monosynaptic projection from the contralateral motor cortex and that the effectiveness of this connection was in both cases much greater than would have been expected from data obtained in monkeys and from earlier observations in man. A further finding was the presence of a slower, possibly indirect and bilaterally distributed pathway from the cortex to these proximal arm muscles, in addition to the prominent monosynaptic one.

METHODS

Six normal male subjects, aged 25–38 yrs, were studied. All gave their informed consent and the procedure had the approval of the local ethical committee. Four had at least two separate studies, which included observations on single motor units in both the muscles investigated. Magnetic and electrical stimuli were used as they appear to excite the brain at different sites (Day *et al.*, 1987b). All subjects had at least one single unit studied with both magnetic and electrical stimulation. The general techniques are similar to those that have been described in detail elsewhere (Day *et al.*, 1989).

Electrical stimuli ('anodal' stimulation) were applied through 2 silver-silver chloride electrodes, attached to the scalp by collodion with the cathode over the vertex and the anode 7 cm laterally, contralateral to the muscle under study (usually over the left hemisphere). The stimulator was a prototype which was capable of delivering a pulse with a maximum amplitude of 750 V and decaying exponentially with a 50 μ s time constant. The magnetic stimuli were generated by a Novamatrix Magstim 200 with a 9 cm coil which was always positioned with the coil horizontal and centred over the subject's vertex. Viewed from above, current flow in the coil could be either clockwise or (if turned over) anticlockwise. Clockwise current flow is more effective in exciting the corticospinal outflow from the left hemisphere and anticlockwise that from the right (Hess *et al.*, 1987). The output of both stimulators was adjusted with a linear controller which read in percent of maximum. Stimulus intensities were generally set to be 10–20% greater than the unit's apparent threshold.

Single motor unit activity was recorded using a conventional concentric needle electrode during a gentle background contraction. For the deltoid, the usual site was lateral to and 6–8 cm below the acromion. In each of 2 subjects units were also recorded from both the anterior and posterior parts of the muscle. For recordings from pectoralis major, the needle was inserted halfway down and just medial to the anterior axillary fold. The needle electrode was adjusted until only one unit was present or clearly dominated any other activity and a window discriminator was used to generate logic pulses when the unit fired. There was a minimum delay of 2 ms before the window discriminator generated a pulse and this has not been subtracted from the histograms illustrated. Direct measurements allowed the absolute latencies to be determined for many of the units and in these cases both uncorrected and corrected latencies are given. The unit amplitude, the levels of the discriminator and the pulses generated were all monitored continuously while the histograms were collected. The proximity of the recording site to the stimulators meant that the records were prone to stimulus artefact. This interference could take two forms, either causing a spurious peak at the time the stimulus was given or effectively disabling the window discriminator for a few ms afterwards. The periods affected by artefact were well before genuine excitability changes began and, where relevant, are noted in the figure legends.

Poststimulus time histograms (PSTHs) were collected with bin widths of 0.25 ms and with 100 repetitions of the stimulus under study. Data collection began 30 ms before the stimulus and continued until 100 ms afterwards, but in this report only events occurring up to 50 ms after the stimulus will be considered. Stimuli were repeated every 3–4 s while the subjects attempted to keep a constant rate of unit discharge, about 10 Hz, with the aid of auditory feedback. The histograms were generated on an Olivetti M280 computer, using a 1401 interface unit (CED Electronics) and associated commercial software, modified to allow immediate deletion of unsatisfactory trials. Timing pulses and unit discharge were also recorded on an FM tape recorder (Store 7DS, Racal Recorders, tape speed 7.5 in/s) for later analysis if necessary.

Peaks in the histogram were identified using the criteria of Day *et al.* (1989) who used similar recording conditions and defined a peak as occurring when there were 4 or more counts in 2 adjacent bins. Half a bin width has been added to the latencies. The durations of peaks have been read directly from the bin timings and the amplitude has been defined as the sum of the counts in the individual bins which make up the peak. Cusum analysis has been used to estimate the number of discharges expected at any given interval after the stimulus (Ellaway, 1977). In this way it was possible to determine whether peaks following the earliest period of excitation represented a real increase in the activity expected (true excitation) or were merely due to recovery of normal excitability (postinhibitory rebound).

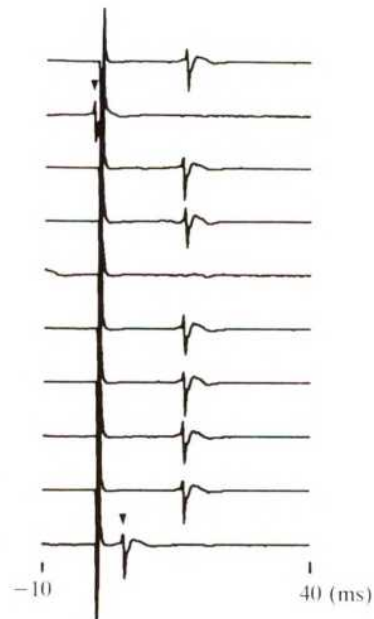
RESULTS

Electrical anodal stimulation

Deltoid. Twelve motor units were studied from the deltoid muscles of 5 volunteers using an average intensity of 61% of the stimulator's maximum. In 4 of the subjects, threshold levels for excitation of the deltoid during a weak contraction had been previously determined using surface electromyography (EMG). For these subjects, the stimulus intensity used when the histograms were collected was on average 24% greater than the threshold value from surface recordings.

All subjects showed a narrow, short-latency peak in the histograms of unit discharge (figs 1, 2). This peak, the earliest period of excitation for all units, will be referred to as 'P0' (Day *et al.*, 1989). The average latency of the peak from the time of the stimulus was 16.1 ms (uncorrected) or 12.7 ms (corrected; based upon direct measurements available for 10 of the units of the time from unit onset to the discriminator pulse output). The peak was narrow, with a mean width of 1.2 ms. The average number of discharges occurring during the peak was 55 ± 15 (mean $\pm$ SD). With one exception, there were no further excitatory peaks, even using high intensity stimulation (fig. 3). The sole exception was a unit from 1 subject in whom the first peak was followed, 5.25 ms later, by another, 0.75 ms wide (this subject also had an unusually small initial

FIG. 1. Recording of a single motor unit from the lateral aspect of the right deltoid muscle, following anodal electrical stimulation over the left motor cortex at 45% of the stimulator's maximum output. Ten successive single trials are shown, with the stimulus being given at the time of the artefact. Note the preferred latency of discharge, 14.3 ms after the stimulus. In 2 of the 3 trials in which the unit did not discharge at this interval it was probably unable to do so due to having been spontaneously active shortly before (arrowheads).



peak containing only 21 counts, while all the other subjects had total counts of 40 or more). The 4 units from the anterior and posterior parts of the deltoid had responses similar to the lateral part and have been included in the average results.

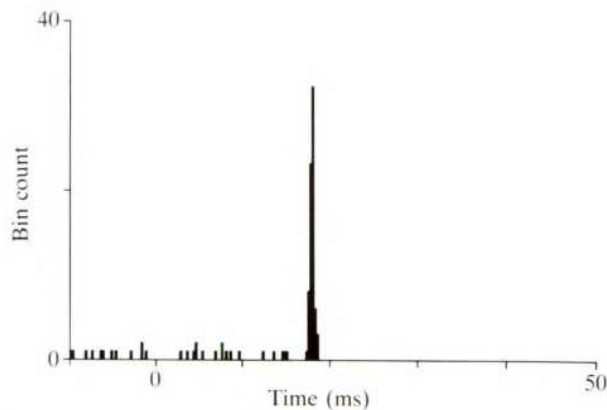


FIG. 2. Same recording as fig. 1 but now displayed as a histogram of 100 trials. The abscissa (in this and subsequent similar histograms) shows the time interval from 10 ms before the stimulus, given at time 0, to 50 ms afterwards. The ordinate shows the number of discharges which occurred during each bin. The preferred interval now appears as an obvious peak beginning at 17.5 ms and lasting 1.25 ms, containing 72 counts. After the peak there is silence for the remainder of the histogram. This pattern was typical of the response of other deltoid units to anodal electrical stimulation of the cortex. (The discrepancy between the latency measured from the histogram and that from direct recordings is due to the method of spike discrimination. The delay is due to the time required for the action potential to exceed the threshold amplitude, plus a further 2 ms.)

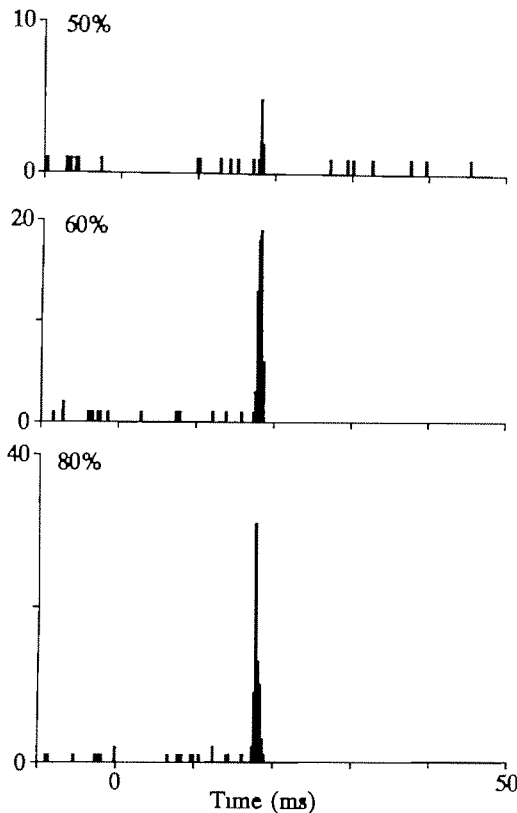


FIG. 3. Three histograms of the response of a single motor unit in the lateral aspect of the left deltoid muscle to different intensities of anodal electrical stimulation over the right motor cortex. Different subject from fig. 1. The uppermost histogram shows the effect of a stimulus of 50% of maximum: a small peak is present consisting of only 7 counts. A small increase in the stimulus intensity, to 60% of maximum (middle histogram), causes a marked increase in the size of the peak to a total of 59 counts. A further increase in the stimulus to 80% of maximum (lowermost part of figure) caused only a modest increase in the size of the peak (69 counts). At no stimulus intensity were any additional peaks of activity present. Abscissa throughout as for fig. 2, but ordinate ranges differ for each of the 3 histograms as indicated. In the final histogram, the apparent reduction of counts immediately after the stimulus is given is probably spurious, as a result of the falling phase of the stimulus artefact adding to the motor unit potential, elevating it above the window of the discriminator.

Pectoralis major. Six motor units from the pectoral muscle were studied in 5 subjects using an average stimulus intensity of 81% of maximum. In 4 of these subjects, threshold stimulus intensities had been previously determined using surface recordings during weak contractions; for them the stimulus intensities used for the histograms were on average 57% greater than the surface threshold values. In all subjects, a narrow, short-latency peak was present (P0, mean duration 1.1 ms, mean latency, uncorrected, 15.7 ms; fig. 4). The size of this peak (mean amplitude 21.7 ± 5.9 counts) was less than half the average size of the corresponding peak in deltoid ($P < 0.01$, unpaired Student's *t* test), despite the higher stimulus levels used for the pectoral units. Three of the 4 subjects who had recordings from both muscles showed a much smaller peak for the pectoral unit.

The histogram shown in fig. 4 illustrates a further point of difference from the findings in deltoid. Unlike deltoid, it was common to find that anodal stimulation produced activity in pectoralis motor units after the initial peak. This additional activity occurred in 2 separable intervals following P0. In 3 of the 5 subjects, a smaller narrow peak followed the first at a mean interval of 3.9 ms; similar activity in other muscles has been attributed to repetitive discharges of corticospinal fibres (i.e., I waves; Day *et al.*, 1989). In 2 subjects, including the 1 illustrated, there was a third period of excitation, beginning more than 10 ms after P0. In 2 others there was some activity at this interval but it

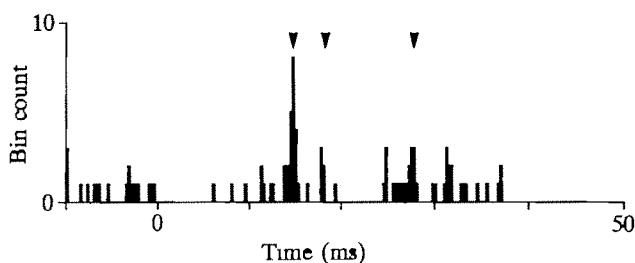


FIG. 4. Same subject as fig. 1, showing a histogram of the discharge of a single motor unit in the right pectoralis major muscle in response to electrical stimulation over the left motor cortex (anodal at 80% of the maximum output of the stimulator). The arrows show peaks of excitation by the criteria of Day *et al.* (1989), used here. Despite the stimulus intensity (80% of the stimulator's maximum) only a relatively small initial peak is present (uncorrected latency, 13.9 ms, total counts 22). This peak, unlike the deltoid unit in fig. 2, is followed by 2 further periods of excitation; the first occurs 4.0 ms after the initial peak, contains 5 counts and may be the result of I wave activity (*see text*). A third period of increased firing is present, but only the 3 bins beginning at a latency of 27.4 ms (13.5 ms after P0, total contents 8 counts) indicate excitation by our criteria. This last period of excitation occurs at a time when reduced firing would be expected to occur (*see Discussion*). Cusum analysis confirmed that this was true excitation and not 'rebound'. A peak due to the stimulus artefact at time 0 has been deleted and the apparent reduction of counts immediately after the stimulus is given is likely to be spurious.

was not sufficient to reach our criteria. We have termed activity at such intervals after P0 'medium latency' excitation as it is likely to have a different origin from the earlier peaks (*see Discussion*). In general, the medium latency was more clearly demonstrated with magnetic stimulation and is discussed in more detail below.

Magnetic stimulation

Fifteen motor units (all from right-sided muscles; 9 from deltoid and 6 from pectoralis) were studied with both clockwise and anticlockwise magnetic stimulation, often at several intensities. All these units were also studied with anodal (electrical) stimulation. For all motor units studied, the earliest period of excitation was always later with magnetic than with anodal stimulation, and clockwise magnetic stimulation usually caused shorter latency excitation than anticlockwise.

Deltoid. For the motor units from the deltoid, both forms of magnetic stimulation usually evoked one or more excitatory peaks, with latencies up to 8.75 ms longer than with anodal stimulation (fig. 5). Clockwise stimulation (at a mean intensity of 56% of maximum) caused up to 5 excitatory peaks (median 2), the first being on average 1.3 ms later than P0. Anticlockwise stimulation (mean intensity 67% of maximum) evoked up to 3 excitatory peaks (median 2) but the first began on average 2.8 ms later than P0. For both forms of magnetic stimulation, these early peaks were narrow (mean width 1.0 ms) and contained an average of 17 counts. When the latencies of each of the excitatory peaks produced by magnetic stimulation were compared with P0 for the same motor unit, preferred intervals were evident, with clustering around times 1.0–1.5 and 4–5 ms later than P0 (fig. 6).

In one motor unit from the lateral aspect of the deltoid and in both units from the anterior aspect of the muscle, anticlockwise magnetic stimulation caused a further period of excitation at medium latency, beginning 9.75–13.25 ms after P0.

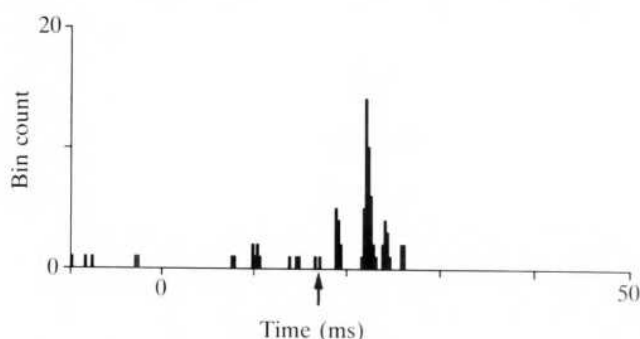


FIG. 5. Single motor unit from the right lateral deltoid muscle in a subject not previously illustrated. The histogram shows this unit's response to magnetic stimulation over the vertex at 55% of the stimulator's maximum output. Current flow was orientated clockwise. The arrow shows the latency for excitation following anodal stimulation over the left motor cortex. As shown here, magnetic stimulation caused multiple excitatory peaks in the deltoid. This unit showed 4 peaks, with latencies from 1.75 to 8.75 ms after the first peak with electrical stimulation (defined as P0; see text). Note the longer gap between the first and second peaks than between the later ones (see fig. 6).

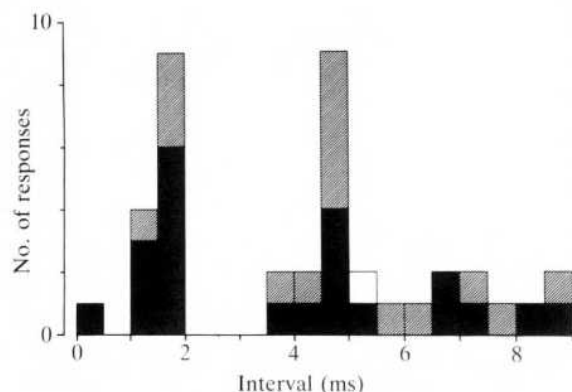


FIG. 6. Histogram summarizing the intervals between P0 and subsequent short-latency excitatory peaks with magnetic stimulation for motor units from the deltoid. Zero time (P0) is defined as the latency of the earliest peak of excitation, in these studies always occurring with anodal stimulation. Results for all subjects have been combined. The ordinate indicates the number of responses which began at the given interval after P0. All recordings were made from the right deltoid and results for clockwise-orientated magnetic stimulation are shown as filled bars and for counter-clockwise as cross-hatched bars. The one open bar is from the 1 subject who showed 2 excitatory peaks with electrical stimulation. The figure shows that latencies with both forms of magnetic stimulation clustered around intervals 1.5 and 4.5 ms later than P0. There is a striking lack of responses starting 2.0–3.5 ms after P0 (corresponding to P2 of Day *et al.* (1989), their fig. 2). The figure also shows that only 1 motor unit was excited by magnetic stimulation within 1 ms of P0, and this came from the posterior part of the deltoid.

Pectoralis major. Despite higher average intensities (clockwise 71% of maximum on average, anticlockwise 74% of maximum), magnetic cortical stimulation evoked fewer short-latency excitatory peaks in pectoral units compared with the deltoid. Clockwise stimulation caused at most 2 peaks at short latency and anticlockwise frequently none in this interval. One subject's motor unit showed no periods of excitation despite maximal amplitudes of both clockwise and anticlockwise stimulation, although the same unit was excited by anodal stimulation. The first period of excitation occurring with magnetic stimulation had an average latency 3.3 ms (clockwise, 5 units) and 4 ms (anticlockwise, 2 units) greater than the onset of excitation after anodal stimulation. There were too few peaks to detect preferred latencies. (Not only were the earliest excitatory effects

weak, but both forms of magnetic stimulation appeared to cause some inhibition in the period just after P0 (e.g., fig. 7). This suppression could be seen with intensities of stimulation below threshold for any preceding excitation and also occurred in the 1 subject who showed no excitatory response to magnetic stimulation. In the subject illustrated in fig. 7, the period of suppression evident in the figure was not present when he was stimulated at the same intensity over the occiput or when the coil was simply discharged near his ear.)

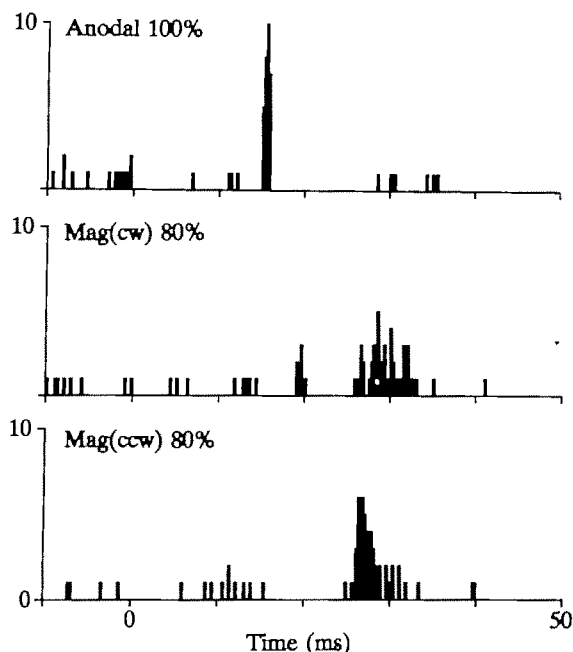


FIG. 7. Histograms for a single motor unit from the right pectoralis muscle, in response to anodal and both types of magnetic stimulation. Same abscissa and ordinate for all 3 histograms, the ordinate indicating the number of counts in each bin. Stimulus artefacts occurring at 0 time have been deleted and these are probably responsible for the lack of counts in the first few ms after the stimulus was given. Anodal stimulation causes the earliest peak (P0, uncorrected latency, 15.1 ms, total counts 30). Clockwise magnetic stimulation (*middle histogram*) causes a small excitatory peak beginning 4.5 ms later and then a further period of excitation beginning at 26.6 ms (uncorrected). This lattermost period, by our criteria, consists of 3 peaks, each separated by less than 1 ms. The *lowermost histogram* shows the effects of counterclockwise magnetic stimulation, at the same intensity as for the histogram above. Note that no short-latency excitation is present; instead, there is a period of reduced firing just after P0. The first period of excitation with anticlockwise stimulation begins at 26.1 ms (uncorrected), 11 ms later than P0, and is significant by our criteria for a duration of 3 ms (total 44 counts). Cusum analysis confirmed that the counts could not be explained by 'rebound'. The two forms of magnetic stimulation were about equally effective in causing the later (medium latency) period of excitation and do so with similar latencies. Note the overlap of the medium latency excitation in the lower two histograms with the later counts in the histogram for electrical stimulation and also the importance of recording the effects of different stimulus modalities.

In contrast to the relatively weak short latency effects, 5 of the 6 units recorded from the pectoral muscle showed a medium latency period of excitation with magnetic stimulation; 2 of these had shown excitation at similar latency following anodal

stimulation. Unlike the earlier period of excitation, the medium latency activity was usually well elicited by both orientations of the magnetic coil; as a result, in 3 motor units (including that shown in fig. 7) the earliest excitation with anticlockwise stimulation occurred during this medium latency period. By our criteria, the period of medium latency excitation on average began 9.8 ms after P0 and ended 13.4 ms after P0 (range up to 15.5 ms after P0). It consisted of 1 or more excitatory peaks (median 2; average duration 1.6 ms) containing up to 44 counts (mean 17). In all cases cusum analysis confirmed that this period of excitation was not the result of a rebound increase in firing after inhibition.

The 3 deltoid units referred to above showed one or more peaks of excitation over a similar period, beginning on average 11.8 ms after and ending 17.2 ms after P0.

DISCUSSION

Before the development of noninvasive methods of stimulating the brains of normal volunteers, observations of the outflow of the human motor cortex were restricted to direct intraoperative stimulation (Foerster, 1936; Penfield and Boldrey, 1937; Rasmussen and Penfield, 1947; Woolsey *et al.*, 1979). In general, these studies appeared to support the distal predominance suggested by recordings in monkeys; thus the area of motor cortex associated with individual fingers was large and greater than that for other parts of the arm. Although these studies were seminal to the understanding of the human motor cortex, their results cannot necessarily be accepted as definitive. Clinical considerations meant that only a limited number of sites could be explored in any one patient. Movements rather than activity in the muscles that caused them were recorded (a finger movement, for example, might be the result of the action either of an intrinsic hand muscle or a finger flexor or extensor in the forearm). The usual stimulus conditions used (repetitive trains with the patients relaxed) would be expected to result in the thresholds being lowest for muscles with well-developed I waves (Patton and Amassian, 1960; and below). Finally, the buried portion of the precentral sulcus, which in man is greater in area than that on the exposed surface (Woolsey *et al.*, 1979), has rarely been explored. The noninvasive methods used in the present study avoid several of these limitations and have the potential to refine these early descriptions.

Responses to anodal stimulation

Anodal stimulation always caused the earliest excitation in the motor units studied. Previous recordings using surface EMG have shown that the central motor conduction time from motor cortex to motoneurons innervating proximal muscles is extremely short, and compatible with a direct monosynaptic linkage (e.g., Gandevia and Plassman, 1988). We found that the initial PSTH peak evoked by anodal stimulation was narrow, 1.1–1.2 ms, and shorter than that recorded for the first dorsal interosseous muscle (Table). This short duration, indicative of the rise time of the underlying EPSP (Ashby and Zilm, 1982; Fetz and Gustafsson, 1983), provides additional support for the presence of a monosynaptic projection from the brain to the motoneurons innervating proximal arm muscles.

The size of the initial peak of the PSTH was large, bringing the motor units from the deltoid to threshold on 55% of the trials and the motor units in the pectoralis major

TABLE COMPARISON OF THE EFFECTS OF CORTICAL STIMULATION ON THREE UPPER LIMB MUSCLES*

Muscle	Mean Cm EPSP size	Rise time	Short latency peaks	Threshold (active/relaxed)	Medium latency effects
First dorsal interosseous	5.0	1.5 ms	2	40/47.5	?**
Deltoid	5.5	1.2 ms	1	50/62.5	+
Pectoralis	2.2	1.1 ms	2	52.5/70	++

* Data from Day *et al.*, 1989. The first 4 columns summarize the effects of anodal stimulation. The first 2 consist of the mean size and rise time of the underlying corticomotoneuronal (Cm) EPSP (mV), estimated from the initial peak on the PSTH. The next column shows the median number of short-latency peaks, including the earliest (P0). The fourth column gives the average threshold levels (expressed as percentage of maximum output of the stimulator) for these muscles for 2 subjects with surface EMG recording during gentle activity and during relaxation. Note that the differences in threshold between the muscles is less marked during activity. The final column refers to the effects of both anodal and magnetic stimuli and indicates the presence or absence of excitation at medium latency with either stimulus. ** No medium-latency effects were commented upon in the original study but on review, weak but definite excitation was present at the appropriate latency in at least 2 of 32 units studied.

to threshold on 22% of all trials. Clearly, the short latency connection from the cortex to these muscles was functionally powerful. The size of the peak can be used as an indirect estimate of the EPSP amplitude in the motoneurons. Assuming that the membrane potential follows a linear ramp trajectory between consecutive action potentials, the EPSP evoked by anodal stimulation would be, in the deltoid, 55% of the total excursion of the potential (Ashby and Zilm, 1982). The excursion between successive action potentials is approximately equal to the threshold for depolarizing the neuron and in cat motoneurons this averages about 10 mV (Eccles, 1964). Thus an estimate of the average EPSP evoked in deltoid motoneurons would be 5.5 mV and in pectoral motoneurons 2.2 mV. These values compare with previous estimates of 3–5 mV for the projection of the first dorsal interosseous muscle using similar techniques (Day *et al.*, 1987a, 1989; Table).

Direct measurements of the size of cortically-evoked motoneuronal EPSPs have never been made in man, but are well documented from intracellular recordings in the monkey. With supramaximal stimulation of the cortex or pyramidal tract, the largest EPSPs are in the order of 3 mV and occur only in motoneurons supplying intrinsic hand muscles or extensor digitorum communis (Clough *et al.*, 1968). In motoneurons supplying biceps or triceps, more proximal muscles, the average values are smaller, and usually less than 1 mV (Phillips and Porter, 1964). Our measurements in man thus suggest that the size of the cortically-evoked EPSP in human spinal motoneurons is larger both in those supplying proximal as well as those to distal muscles when compared with monkeys. Three important points should be considered along with this conclusion. First, because of limitations in the technique, the cortical stimuli used were not supramaximal and thus our estimates of EPSP size may be too low. Secondly, the absolute size of the EPSP depends upon the membrane potential depolarization and its trajectory; depending upon the curvature, a nonlinear depolarization may lead to either an over or under-estimation of the true EPSP size. Systematic differences in these parameters between muscle groups is a remote possibility, although this would not alter the evidence of functional effectiveness of the projection. Finally, the present technique samples activity in low-threshold, therefore small, motoneurons (Henneman *et al.*, 1965) whereas microelectrode techniques are biased towards large motoneurons. Clearly, EPSPs may

differ between motoneurons of different sizes. However, in a study in the monkey, this effect was variable and usually not statistically significant (Clough *et al.*, 1968).

Anodal stimulation of the brain was capable of causing more than one peak of increased firing probability in PSTHs of pectoralis major motor units. Direct recordings in monkeys have demonstrated that single cortical shocks usually generate multiple volleys in rapidly conducting corticospinal fibres (Kernell and Wu, 1967a). The earliest volley, the D (direct) wave, is followed by one or more I (indirect) waves and a corresponding series of EPSPs can be recorded in spinal motoneurons (Kernell and Wu, 1967b). Multiple descending volleys have been recorded from the spinal cord in man after anodal transcranial stimulation (Boyd *et al.*, 1986; Inghilleri *et al.*, 1989), the first of which is consistent with direct activation of corticospinal neurons: here we have assumed that P0 is a measure of the latency of the EPSP generated by the D wave. It is of interest that there was usually only a single peak in the PSTH from deltoid motor units. Although the reason for this is uncertain, it may explain one puzzling phenomenon. Although the initial EPSP evoked by cortical stimulation in deltoid motoneurons appears to be as large as that in the first dorsal interosseous, the threshold for recruitment of the deltoid in relaxed individuals is usually greater (Table). A single compound EPSP alone should not be sufficient to depolarize a relaxed motoneuron to threshold; however, EPSPs at short intervals such as those generated by D and subsequent I waves can summate and become suprathreshold (Kernell and Wu, 1967b; Muir and Porter, 1973). It follows that a large initial depolarization alone, although indicative of a powerful corticospinal projection, will be considerably less likely to discharge the target motoneuron than the same initial EPSP followed by further short-latency depolarizations.

Responses to magnetic stimulation

We have confirmed that as in the hand muscles, the first responses evoked by magnetic stimulation in deltoid and pectoralis occurred at latencies greater than the responses to anodal stimulation. More than one peak of increased firing probability often occurred following magnetic stimuli and in the deltoid there was clustering around preferred intervals 1–2 ms and 4–5 ms following P0 (defined by anodal stimulation). These peaks are probably analogous to P1 and P3 reported for the first dorsal interosseous muscle by Day *et al.* (1989), which they argued were due to the arrival of the I1 and I3 waves in the pyramidal tract. In the present experiments, occasional further early peaks were seen, beginning up to 8.75 ms after P0. Exceptionally, up to 5 I waves can be generated by cortical stimulation in monkeys (Kernell and Wu, 1967a). We propose therefore that activity beginning at latencies less than 9 ms in excess of P0 could be explained by I wave activity.

A new finding was the presence of a period of medium latency excitation in the PSTH, beginning roughly 10 ms later than the earliest effects with anodal stimulation. This excitation was not simply a rebound increase in firing after a period of inhibition, but represented a true extra facilitation of motor unit activity. It was most clearly seen in pectoralis major, perhaps because of the smaller preceding PSTH peaks in this muscle; peaks in the PSTH should be followed by a 'shadow' of reduced firing probability, the duration of which is proportional to the height of the peak (Ashby and Zilm, 1982). The medium latency facilitation was not dependent upon the presence of earlier excitatory peaks and could occur in the absence of any preceding facilitation. Our results do not

allow a definite conclusion as to its basis. Anatomical evidence suggests at least two possibilities: activity in small diameter corticospinal fibres, excited transsynaptically, could be responsible with the greater latency a result of their slower conduction velocities; alternatively, an indirect polysynaptic route may be involved, for example, a cortico-bulbospinal pathway (Kuypers, 1981). It is notable that the threshold for eliciting this medium latency excitation was similar for both clockwise and anticlockwise orientations of magnetic stimulation, in contrast to the earlier, short-latency excitation. For the short-latency responses, clockwise current flow in the coil activated the large corticospinal fibres of the left cortex more effectively than anticlockwise current and vice versa. The observation that the current orientation had little influence on the threshold for the medium-latency responses could be simply explained by a projection with a bilateral organization, either cortical or subcortical. If, for example, the fibres responsible for the medium-latency period of excitation were to originate equally from both hemispheres then, even if each orientation of magnetic stimulation were to activate predominantly a single hemisphere, the sum of the excitation arriving at the spinal level would be identical for both clockwise and anticlockwise current flow. Inputs originating from both hemispheres have been proposed for arm muscles in man and may be particularly marked for the shoulder adductors (Colebatch and Gandevia, 1989).

Our findings potentially have both physiological and clinical significance. We have found evidence supporting the presence of a corticomotoneuronal projection to proximal arm muscles, a projection that differs significantly in strength between two antagonistic muscles acting at the same joint. The existence of such potent corticomotoneuronal projections to proximal arm muscles in man may be related to the human ability to make fast and accurate contractions of these muscles when used for example in throwing or reaching. Another consequence of the strength of this input is likely to be the relatively severe involvement of shoulder muscles, and the deltoid in particular, in human stroke when compared with experimental lesions in lower primates. Proximal arm weakness following unilateral cerebral lesions has additional features which suggest that the muscle innervation is in part bilateral (Colebatch and Gandevia, 1989): the medium-latency excitation may be a result of activation of the pathways responsible.

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NOTE ADDED IN PROOF

Since this paper was accepted for publication, it has become apparent that the direction of current flow in the magnetic stimulating coil is opposite to that described here (see Erratum in *Journal of Physiology, London* (1990) **430**). Thus, wherever we have designated coil current as clockwise, this should be amended to counterclockwise and vice versa.

OCULAR MUSCLE PROPRIOCEPTION AND VISUAL LOCALIZATION OF TARGETS IN MAN

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SUMMARY

Passive deviation of one eye through 18°, 30° and 42°, achieved by force applied to a sucked-on contact lens, caused the direction of visual targets seen by the other eye to be misjudged in the direction of the passive movement by an amount roughly one-sixth of the angle of passive deviation. The result was the same when the perceived direction was indicated by hand, as when the instant at which a moving target seemed straight ahead was signalled. This result is interpreted by considering that muscular efferents were identical in normal and eye-deviated subjects. The main difference between the two target localization conditions results from the proprioceptor output of the deviated eye. Our data demonstrate that the assessment of the direction of a target seen by an eye that is free to move depends in part on information received by the brain from proprioceptors in the orbit (in our case the contralateral orbit). It would be surprising if the ipsilateral orbit did not contribute as much or more. We therefore consider that this constitutes clear evidence against the pure outflow theory of visual direction judgement (Helmholtz, 1867), additional to that provided by the all-or-nothing situation of complete versus incomplete oculomotor paralysis.

Two models have previously been proposed to describe the function of the visual localization mechanism. Both assume that the necessary information is derived from the coding of the position of the eye in the orbit, either through a copy of the muscular activation or through eye muscle proprioception. We propose an alternative model in which both afferent and efferent signals from all actively contracted or stretched muscles provide the necessary information to the CNS. The data gathered so far from normal subjects made strabismic with a suction lens, and from a fair proportion of strabismic patients, support our model describing the mechanism of localization of a single punctate target in darkness.

INTRODUCTION

Helmholtz (1867) gave clear evidence that the information about the direction in which our eyes are pointing and which we use for assessing the direction of a visible object depends on monitoring the messages sent from the brain. Sherrington (1918), solely on the grounds that human extrinsic ocular muscles contain muscle spindles and without answering Helmholtz's contrary arguments, suggested that we use proprioceptive information from sensors in the extrinsic ocular muscles (*see* Milleret *et al.*, 1985, for a review of the literature on direct and secondary central projections of ocular muscle proprioceptors). Mach (1886), Kornmüller (1931), Brindley and Merton (1960), Stevens *et al.* (1976), Matin *et al.* (1982) and Guthrie *et al.* (1983) published new experiments that confirm that outflow information is used, but did not exclude a minor contribution from proprioceptors. Sherrington's view in its pure form has never had any experimental support, but Siebeck (1954) published an observation which made it probable that in

one extreme situation messages from sensors in the orbit can influence the direction of things seen. He found that, in partially curarized subjects, any eye movement causes an apparent displacement of things seen of just the kind that Helmholtz's theory predicted; but in completely curarized subjects he found that attempts at eye movements caused no apparent displacement of things seen. If Siebeck's subjects succeeded in sending impulses out along their oculomotor nerves, this disproves (for an extreme condition) the pure form of Helmholtz's theory. Brindley *et al.* (1976) and Martin *et al.* (1982) extended Siebeck's experiment to unilateral paralysis. They showed that during an attempted eye movement, things seen by an eye whose extrinsic muscles are completely paralysed by retrobulbar injection of local anaesthetic appear stationary, although, if the paralysis is incomplete, they move as predicted by Helmholtz's theory. Here there is no doubt that the subjects succeeded in sending impulses out along the oculomotor nerves because the nonparalysed eye moved. The subjects' brain must have used proprioceptive signals indicating that the paralysed eye had not moved to override the outflow signal that falsely indicated that it had moved.

It seems that until now the only published evidence indicating that proprioceptive information from the orbit is used in assessing the direction or movement of seen objects concerns the above all-or-nothing condition. We present here evidence that under very different conditions proprioception contributes a part, although not the main part, of the information that the brain uses to determine the position of the eyes for the purpose of assessing the direction of seen objects.

The motivation for carrying out this study originated from observations conducted on strabismic patients. We have observed that all strabismics tested responded in a manner different from normal subjects in a visual open-loop pointing task (Mandelbrojt, 1986). Among 43 patients, 27 (16 constant and 11 alternating cases) showed an alteration of the same nature considered to originate from oculomuscular proprioception. This study showed that when a normal subject pointed monocularly at a visual target placed in front of him with his unseen index finger (open-loop condition) he usually made no localizing errors. If he did, the error was systematically slightly to the right of the target if the right hand was used or to the left if the left hand was used to indicate target position (fig. 1A). This was true whether the right or left eye was used. However, some strabismics (alternating and constant, either eso or exodeviated) were seen to make large errors, systematically in the direction of the nonfixating eye, whether the fixating eye was the normal or the strabismic eye and whether the left or right hand was used. For example, an exodeviated strabismic, fixating with his right eye, pointed to the left of the target with his right hand (fig. 1B), while when fixating with the left eye, he produced a large error to the right of the target.

This observation, which applied to about 65% of the patients studied, suggested the following hypothesis, namely that the visual localization mechanism relies on information derived from both eyes, whether or not both eyes are used to fixate the target. The hypothesis implies that afferent and efferent signals from both eyes combine to provide the perception of the location of an object in space. To test this hypothesis we therefore induced strabismic-like deviations in normal subjects by means of a suction scleral lens. The results confirmed that sustained mechanical deviation of one eye which was covered, induced mislocation of a target viewed by the normal eye. The error was in the direction of the mechanical deviation.

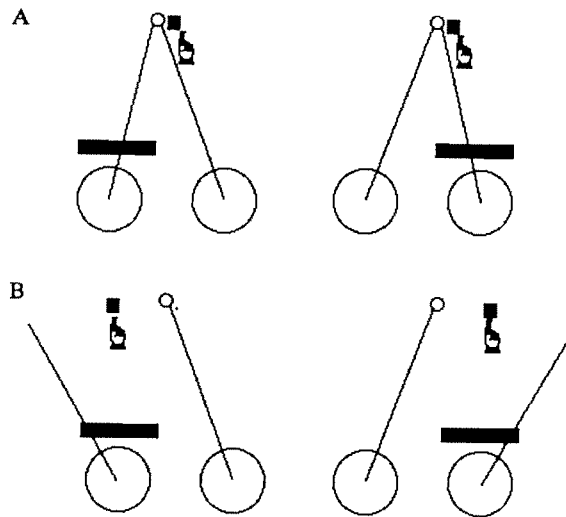


FIG. 1. Localization of a target as indicated by the hand. A, normal subjects localized a target with a small error, identical in direction and amplitude whether the right or left eye was used for viewing. B, some strabismics showed an error, in localizing a target with the right hand, systematically in the direction of the deviated eye, with either right or left eye viewing. Open areas = actual target position, closed areas = hand-indicated target position.

In order to exclude a possible bias effect of eye muscle stretching on the hand motor control system, a second set of experiments was designed to evaluate the effect of the mechanical deviation of the covered eye on the perceived position of a target as indicated by the fixating eye. In this experiment, the subject was requested to signal the experimenter when he perceived, as being straight ahead, the position of a slowly moving target along a horizontal direction. The experimenter recorded the corresponding target position. The effect of the mechanical deviation was established by comparison with the perceived straight ahead direction in the monocular, otherwise normal, viewing condition.

Analysis of the data suggests that localization of a punctate target in total darkness is obtained by combination of binocular outflow afferent and inflow efferent information, whether monocular or binocular viewing is used. When proprioception was altered by mechanical deviation of the nonviewing eye, a centrally presented target was mislocated in the direction of the sustained deviation of the covered eye and the perceived straight ahead direction appeared shifted in the same direction by about an equal amount.

METHODS

There were two experiments. In the first the subjects were required to indicate by hand the perceived position of a monocularly presented target. In the second, they were required to indicate when a moving monocularly presented target was straight ahead. Five volunteers, ranging in age from 22 to 48 yrs, were selected for the study. They gave informed consent after being presented in detail with the aims of the study and the experimental procedures. All had normal vision without correction. They were examined by a physician before the experiment and referred to the optician who prescribed the lenses. Two other subjects were excluded after preliminary tests in normal monocular viewing conditions because of their excessive intra and intertest variation and systematic error.

Experiment 1: Visuomanual localization of a target

The ability of the subjects to indicate the perceived position of target was quantified by means of a technique commonly used in prism adaptation studies (Held and Gottlieb, 1958). In this technique, the subject is asked to indicate with his index finger (or a pencil) the perceived position of a visual target presented within easy reach of the upper limb. Our experimental arrangement was a modified version of that designed by Mandelbrojt *et al.* (1984) to study visuomanual adaptation in newly presbyopic subjects. The fully computerized system made use of a Summagraphics BITPAD 90 × 70 cm digitizing table connected through an electronics interface to an IMS 5000 microcomputer. Fig. 2A shows the subject seated in front of the table, the head immobilized at a forward-tilted angle using a bite bar covered with dental wax.

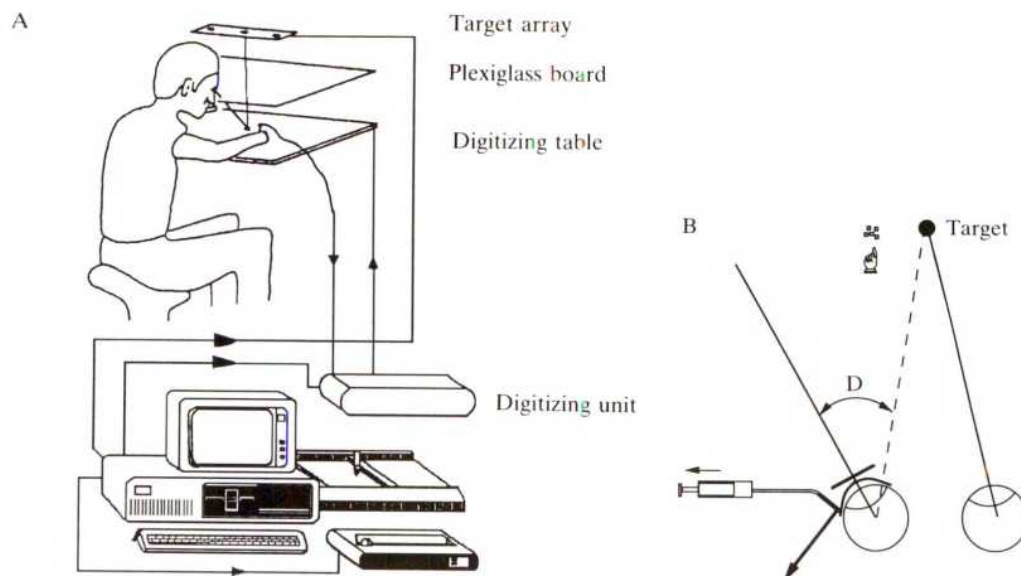


FIG. 2. Experimental arrangement. A, the subject was seated in front of a digitizing table on which virtual targets were presented. He indicated with his hand the perceived position of the targets. B, a suction lens was used to induce a sustained deviation of one eye. The lens was secured to the cornea through a light air vacuum produced by a syringe.

A row of green light-emitting diode (LED) targets was positioned horizontally 60 cm above the table. A glass plate 1.5 mm thick was placed horizontally above the table at such a level that, as seen by the subject, the targets appeared virtually exactly on the surface of the digitizing table. During recording, a thin black board was inserted under the glass plate to further prevent the subject from viewing his forelimb. The use of virtual targets prevented him from gathering tactile information related to target positions. Three target positions were chosen to appear 38 cm from his eyes, along a transverse line about 40 cm away from his chest. One target was exactly in front of the subject and the 2 others at 9 cm (12°) on each side of the centre one. The LEDs were driven by the computer and separately current-balanced to produce the same light intensity. They appeared as well defined green spots, about 2 mm in diameter.

All pointing sessions consisted of a series of 2 to 6 successive sets of trials. Each set was composed of 15 target presentations, randomly appearing at the 3 locations. An algorithm balanced the sets so that each position was selected 5 times for each presentation set. The experiment started with a calibration procedure run with some light illuminating the digitizing table. While each target was turned on once, the experimenter indicated to the computer, with a pointing pencil connected to the control unit of the digitizing table, the exact location of the target.

Each pointing trial was controlled by the computer in such a way that lowering the pencil in a 10×10 cm

zone designated as the starting zone (situated at the right near corner of the table) made one of the targets appear for 800 ms. The subject was instructed to look at it and keep on 'fixating' its position while pointing with the pencil at its apparent position. The pencil had to be pressed onto the table to trigger, via a micro-switch, the computer reading of the pointing coordinates.

The next pointing sequence was initiated whenever the subject returned his hand to the starting zone and lowered the pencil towards the table surface. Subjects were encouraged to point at a moderate but regular pace in rapid ballistic saccadic-like movements. The first touch of the table with the pencil triggered the recording of the coordinates and disabled the entire pointing area except the starting zone.

The experiment was run in total darkness so that the subject, who could not see his hand, was unable to correct for pointing errors. The experimental conditions were varied after each set of 15 trials. A typical series of 3 sets of pointings usually started with a set in normal visual conditions, that is, with binocular or monocular vision but no mechanical deviation of the covered eye, followed by a set of pointings with the lens-fitted eye deviated in one direction. The series ended with a pointing set carried out in normal conditions. The eye deviation procedure is presented in detail in the next paragraph dealing with Experiment 2.

Experiment 2: Perceptual visuo-ocular localization of a target

The subject was seated in the dark room, in front of a horizontal black board using the digitizing table employed in Experiment 1. His head was immobilized in a slightly forward-tilted position by means of a bite-bar. A target, 2 mm in diameter, appeared at a random position to the right or to the left, and started to move slowly along a horizontal line crossing the board. The line was 38 cm away from the subject's eyes. The subject advised the experimenter verbally as soon as he felt the target had reached the straight ahead position. He could request further motion of the target to the right or the left if necessary. The final target position was recorded by the computer and the next trial was initiated. A series of 25 presentations was executed, first in normal monocular viewing conditions and then with the covered eye deviated 30° to the right or to the left by means of a suction lens. The effects of the mechanical deviation of the covered eye were expressed by comparing the average perceived straight ahead direction in normal and eye deviated conditions.

Sustained mechanical deviation of one eye was produced by appropriate traction applied to a scleral lens made to adhere to the globe by light suction produced by a syringe (fig. 2B). The syringe was connected to the lens by light supple tubing, 1 mm in diameter. The custom-made lenses provided by Les Frères Lissac, Marseilles, were equipped with a small tube protruding 3–4 mm on the temporal side of the lens. This tubing was connected to the syringe. A small pivot positioned on the opposite side was used to exert the deviation by means of a thread. In pretest trials, it was found that perfect adherence of the lens to the sclera for a 20–30 min period could be obtained by withdrawing 8 cc over a 25 cc initial volume, including tubing volume.

A reliable and precise 30° mechanical deviation in a given direction was obtained by presenting a target 30° from the centre, in the desired direction. The subject fixated the target while the experimenter exerted a slight additional pull on the thread before securing it to the head frame. The additional pull of the order of 1° produced a diplopia which was used as a definite sign of immobilization at the intended position. Once the thread was secured to the head, the eye deviation experiment started immediately. A check of the immobilization condition was carried out systematically at the end of each experiment. In 2 instances in which the suction was insufficient to keep the lens attached to the eyeball, the data were rejected.

The lens was placed on the eyeball just before the experiment and applied for no more than 25 min. One drop of novesine was applied to the eye before fitting the lens. Whenever a subject reported some discomfort with the lens during a recording session, the experiment was immediately terminated and the data rejected.

Data analysis

The data are presented as 'pointing maps' showing on a single graph all the pointing marks directed towards the 3 targets. The entire plot reproduced on a digital plotter was scaled with a reduction factor given below the graph. The pointing marks were shown for each set of 15 pointings. The successive sets were numbered 1 to 6, individual pointings of each set appearing as corresponding numbers.

The computer calculated the average pointing position for each set of 5 pointings directed towards a given target. The average for each set is indicated by a larger circle positioned at the intersection of lateral

and anteroposterior error. The number within the circle relates to the order of the pointing set. The dispersion of the data was characterized by confidence ellipses which are also shown on the pointing maps. In most figures, insertion drawings depict the experimental conditions for the successive sets of pointings in the up-down chronological order.

RESULTS

Subjective effects resulting from passive rotation of the covered eye

The 5 subjects all showed extensive localization errors induced by deviation of the covered eye. Nevertheless, none of them noticed any change in the conscious perception of the target position as viewed by the normal undeviated eye, either while the covered eye was being deviated or under sustained deviation.

Eye movement monitoring of the viewing eye

One subject was tested in a specifically designed protocol to elucidate this somewhat unexpected observation that all subjects showed localization errors when the covered eye was deviated mechanically. For this, the eye position of the fixating eye was monitored by an infrared corneal reflection technique while the covered eye was being alternately deviated towards or away from the fixating eye. The subject was either fixating the centre target or its remembered position with his normal eye. Under these conditions, no illusory motion of the fixated target was perceived by the subject, and no slow or fast systematically directed eye movements greater than the recording sensitivity (0.1°) were observed either as drifts or as saccades. Nevertheless, when the subject was requested to point at the target while the covered eye was steadily deviated, an error of target location in the direction of the sustained mechanical deviation was observed.

The same subject was also tested several times to determine the time course of the changes in target location induced by mechanical deviation of the covered eye. For this, he performed a series of pointings allowing various durations between the setting of the deviation and the beginning of the pointings. The measures showed that for durations extending from a few seconds to 20 min, the mispointing errors tended to decrease rapidly (while variability increased) as the prepointing period increased. The larger and more systematic effect was obtained with testing immediately following mechanical deviation, while more limited effects and larger data dispersions resulted after prepointing periods of the order of 15 min or longer. A series of experiments is planned to study this phenomenon further.

The effect of a sustained deviation of the covered eye on the perceived straight ahead has only been systematically studied in the horizontal direction. However, we have no reason to suspect that the effect we have observed by pulling the eye in the horizontal direction would not also be generalizable to other directions.

Experiment 1. Localization of a target by pointing

For convenience of presentation and interpretation of the results, one set of data from 1 subject representing the main tendency will be illustrated while averages from the combined individual data will be shown in a more composite form. As mentioned in the Methods section, the effect of sustained eye deviation on localization of a target (and on perceived straight ahead) was systematically determined by comparing the mean

perceived location in normal monocular viewing conditions with the mean perceived location during sustained deviation of the covered eye. Only the errors of localization in the transverse direction will be considered here. Fig. 3 shows such a comparison. In the normal right eye viewing condition, as illustrated in the inserted drawing, 5 pointings were performed to each of the 3 presented targets. Individual pointing marks appear as a numeral 1 (fig. 3A). The average location position for each set of 5 pointings is shown as a 1 centred in the confidence ellipse. As readily observed, the subject located the targets with fairly high precision. The dispersion of the data points was larger for the laterally than for the centrally presented target. Fig. 3B illustrates more average and confidence ellipses for four successive series of pointings carried out under normal viewing conditions to show the reproducibility and reliability of the data.

Fig. 3C shows two sets of pointings applying, respectively, to the normal viewing condition (numeral 1), as in 3A and B, and to the condition in which the right eye was deviated 30° to the right (numeral 2). In normal viewing, the subject showed a slight mislocation of the targets. The systematic error was about 2° for all 3 targets. With the right eye deviated, the perceived location of the central target was 6.2° to the right

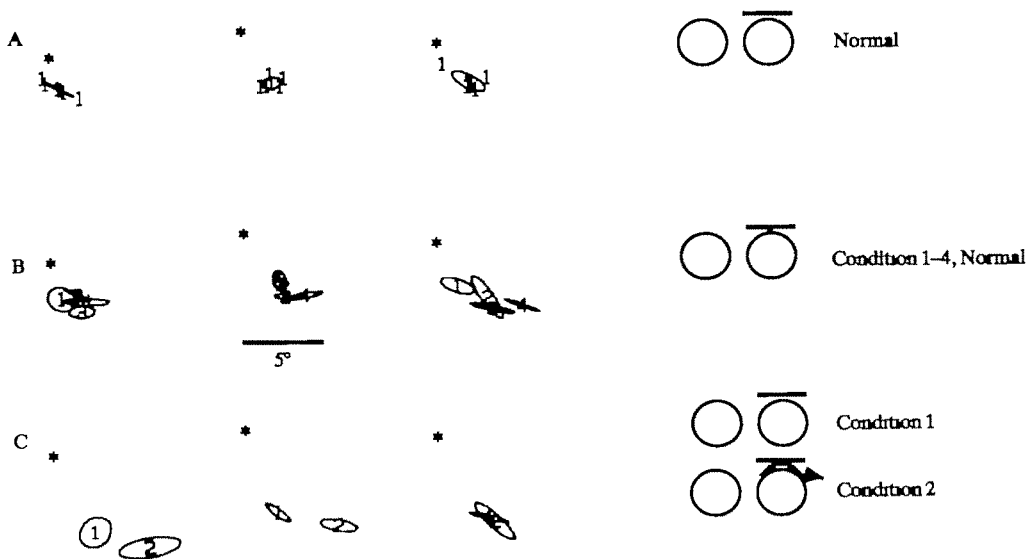


FIG. 3 Typical pointings to three target positions. A, a series of 5 pointings executed towards each target under normal viewing condition is represented showing individual marks, mean pointing positions (as a 1 centred in the ellipse) and confidence ellipses. B, four successive series of pointings in normal viewing represented by average position and confidence ellipses demonstrate narrow dispersion and reliability of data. C, during sustained right eye deviation, the subject mislocated the targets with an error systematically to the right of the perceived target position in normal viewing.

of its actual position. A similar error applied to the left target, but the localization of the right target was only slightly to the right of the perceived position in normal viewing. As also observed in all subjects fig. 3 shows a slightly larger data dispersion in the deviated eye than in the normal viewing condition. As a general finding (*see* fig. 6),

the larger the angular deviation between the two eyes, the larger the localizing error. Since the 30° deviation of the right eye was referred to the head, the misalignment of the right eye was 18° when fixating the target ipsilateral to the eye-pull but 42° for the contralateral target. This allowed us, in a single experiment, to plot a curve describing target localization error as a function of eye misalignment (fig. 6).

Fig. 4 shows the pointing map from a subject submitted first to a series of pointings with the right eye deviated to the left (numeral 1), then to a series with the eye released (numeral 2) and finally a series with the eye deviated to the right (numeral 3). Here too, the direction of the localization errors was systematically in the direction of the sustained deviation.

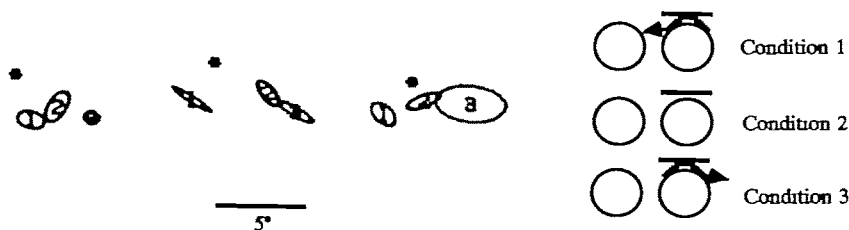


FIG. 4. Right eye deviation. When the right eye was deviated to the left (Condition 1) or to the right (Condition 3) the subject mislocated the target with an error to the right and to the left of the perceived target position in normal viewing (Condition 2).

The observed effect of a mechanical pull applied to the nonfixating eye, in the horizontal direction, was seen to be generalized to the four cardinal directions and possibly to all directions. Fig. 5 illustrates a condition in which the left eye was successively deviated 30° left, right, up and down. Mislocation errors were systematically in the direction of the mechanical pull applied to the covered eye. Here, only the mean pointing positions

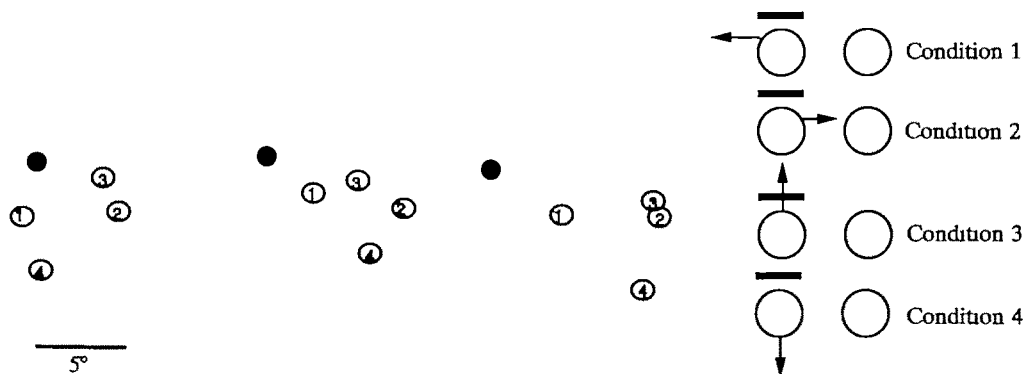


FIG. 5. Mislocation errors induced by left eye deviation to the left (Condition 1), to the right (Condition 2), upwards (Condition 3) and downwards (Condition 4).

applying to each set of 5 trials are represented. The numbers at the centre of the circles indicate the average positions.

There might be an after-effect following the release of the pull such that the pointings performed after a series during which the covered eye was pulled in one direction showed a deviation with respect to the results of the prepull control series. A study is currently in progress aimed at defining the extent and conditions of occurrence of this after-effect.

Combination of the results from the 5 subjects

The effect of a sustained 30° deviation of the covered eye along the horizontal axis was studied systematically in all 5 subjects, but pulls along the vertical axis were only applied on a few occasions. Therefore only data from right and left pulls were analysed statistically; these are combined in fig. 6A. It shows the average mislocation errors

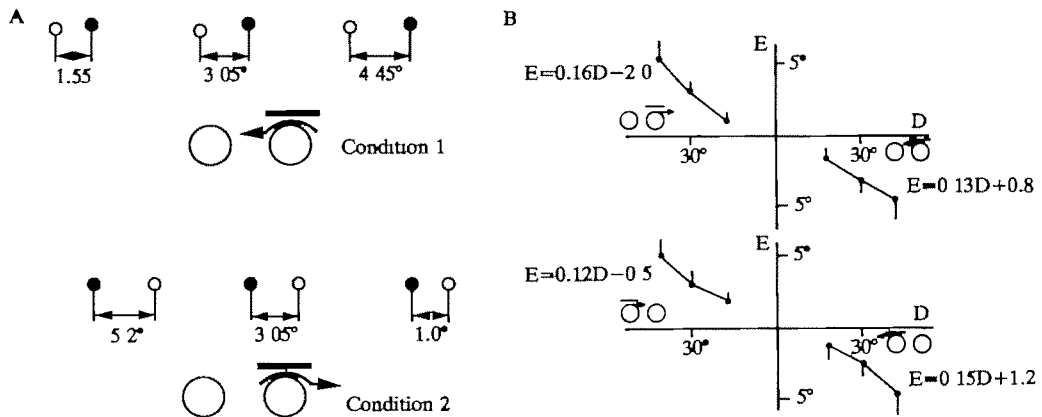


FIG. 6. Average localization error with sustained deviation of the covered eye. A, deviation of the covered right eye induced a pointing error of targets viewed by the left eye. The pointing errors were systematically to the right when the right eye was deviated to the right (Condition 1) and to the left when the right eye was deviated to the left (Condition 2). Filled areas = target positions; open areas = average pointing positions. B, average error (E) as a function of ocular misalignment (D) for the right eye (top) and left eye (bottom). The targets were presented at the centre and 12° to the right and to the left so that a 30° eye deviation with respect to straight ahead resulted in eye misalignments of 18, 30 and 42°. The vertical lines attached to the points are SEMs.

induced as a result of the pull applied to the covered right eye and fixation with the left eye. Similar results (fig. 6B) were obtained with fixation with the right eye and sustained deviation of the left eye. Fig. 6A summarizes the results from 7 runs (2 subjects were tested twice). To clarify the representation, all pointings were normalized by subtracting the average systematic error as measured in pretest runs, so that the effect of the sustained deviation is referred to the actual position of the target, regardless of the individual systematic errors. The inserted drawings help identify the conditions. Fig. 6B plots mislocation error (E) in deg as a function of angular deviation (D) in deg for right and left pulling of the right eye (top) and left eye (bottom). It shows that the error increases more or less linearly with target eccentricity for a given pull. In other

words, there is a roughly linear relationship between the amplitude of the error and the misalignment of the eyes. The following regression equations describe the average effect for sustained right and left deviations of right and left eyes, respectively.

$$E = 0.164D - 1.81$$

$$E = 0.166D - 2.05$$

where E is the pointing error in deg, D is the angular misalignment (deviation) of the 2 eyes in deg.

These equations suggest that below about 10° of misalignment no error is likely to occur or it cannot be revealed statistically.

Experiment 2

A series of 25 measures of the perceived straight ahead direction was made in 4 subjects. One subject who participated in Experiment 1 was excluded from the group because his results were highly variable and showed much larger data dispersion than the other subjects. Fig. 7 shows the average data. The subjects were first tested in the protocol pertaining to Experiment 1 in order to compare, in a single experiment, in the same

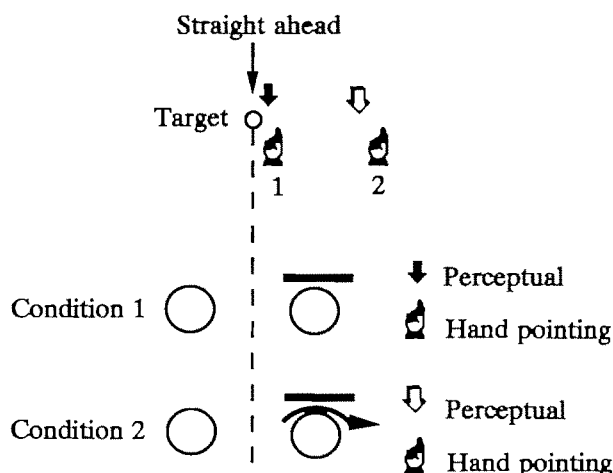


FIG. 7. Perceptual localization of a target as being straight ahead. In the normal condition, the target position was quite accurately indicated by the hand (hand 1) and there was only a small straight ahead position error (black arrow). With the right eye deviated 30° to the right, the subjects identified the position of a centre target as being markedly to the right of the actual target position. The error of position indicated by the hand (hand 2) was slightly larger than the shift in perceptual straight ahead (white arrow).

subject, the perceived location of a centrally presented target as indicated by the hand and the perceived straight ahead. Inserted drawings depict the visual condition and nature of the test. In particular, a hand picture is used to refer to hand pointing and an arrow to perceptual straight ahead.

Before eye deviation, the subjects pointed with their hands to a similar position to their indication of straight ahead. The mean pointing error was 0.8° to the right of the

target while the mean straight ahead was 1.2° to the right. The dispersion of the data was similar.

During sustained deviation of the covered right eye by 30° to the right, the subjects mislocated the central target by 6° to the right. The average perceived straight ahead direction was likewise shifted to the right but by a lesser amount (4.6°) than the perceived position of the target as indicated by the hand. From individual records and from statistical analysis of combined data we found that the dispersion of the pointings (as already observed in Experiment 1) and of the perceived straight ahead was larger than that recorded under normal viewing conditions. This was a general finding in all tested subjects (see Table).

TABLE AVERAGE POINTING ERRORS AND SHIFTS (IN DEG) IN STRAIGHT AHEAD IN NORMAL AND DEVIATED CONDITIONS FOR EACH SUBJECT, AND OVERALL MEANS

Test	Condition	Subject 1 mean error	Subject 2 mean error	Subject 3 mean error	Subject 4 mean error	Mean	SD
Hand pointing	Normal	0.5	2.3	1.4	0.8	1.25	0.8
	Deviated	5.1	4.0	4.7	4.6	4.6	0.45
Perceptual straight ahead	Normal	0.8	2.1	2.0	1.5	1.6	0.6
	Deviated	5.4	6.9	5.8	6.3	6.1	0.65

DISCUSSION

Target localization

Localization of a target in space with respect to the observer requires coding of the position of the eye in orbit. This signal combines with the projection of the target on the retina to provide target position with respect to the head. Several studies conducted with strabismics show that most patients mislocate targets before or/and after surgery on the normal and/or the strabismic eye (Mann *et al.*, 1979; Steinbach and Smith, 1981; Bock and Kommerell, 1986; Gauthier *et al.*, 1986).

Strabismus

A role for ocular muscle proprioception in eye alignment and localization of visual targets in strabismic patients has been suggested by Steinbach and Smith (1981), whereas Bock and Kommerell (1986), using the same approach, provided data which instead supported the outflow model. With regard to the problem of object localization, both inflow and outflow models predict that a strabismic patient is likely to make errors in localizing visual targets, either before and/or after surgery. These errors may arise from mechanical changes in the position of the eye in the orbit, resulting from the surgical alteration of muscle lengths and tendon attachments. Also likely, as suggested by Steinbach and Smith (1981), Bock (1986), Bock and Kommerell (1986) and Gauthier *et al.* (1986), errors may arise from damage to the receptors which are situated in the musculotendinous portion of the muscles; this is the region which is either resected or recessed during surgical intervention. Comparing visual localization ability in primary versus secondary operated strabismics, Steinbach and Smith (1981) concluded that

proprioception was essential for eye alignment and proper localization of visual targets.

We observed in previous experiments (*see* Introduction) that some patients when tested in a hand pointing task behaved in a way which suggests that the nonfixating eye, whether it is the good or the strabismic eye, introduces a bias in the sensing of the position of a monocularly viewed target. The present data confirm our preliminary results (Gauthier *et al.*, 1988a): sustained deviation of one eye in a normal subject resulted in an error of localization of a target viewed by the other eye. The error was in the direction predicted by the model we proposed to account for the observations derived from the experiments with strabismics. The fact that the localization error was of same order of amplitude and in the same direction whether the subject was requested to indicate the target position with his hand or the straight ahead direction suggests that the effect does not involve the hand motor system.

Such effects may contribute to the results of our Experiment 1, but not to those of Experiment 2. The close quantitative similarity between the results of our two experiments suggests that the influence, if any, of passive deviation of the eye on upper limb proprioception in Experiment 1 is small.

Eye pulling could have had an effect on the sensing of hand position; this possibility was suggested by studies in the cat (Easton, 1971, 1972) showing that EMG changes in the upper limb are induced by stretching the eye muscles. Furthermore, biceps vibration in man results in illusory motion of a target (Gauthier *et al.*, 1988b) and tight coupling between eye and hand movement has been demonstrated in man (Gauthier *et al.*, 1988b) and monkey (Miall *et al.*, 1985; Gauthier and Mussa Ivaldi, 1988). Such interactions cannot be involved to explain the mislocation errors that we observed on pulling the covered eye of our subjects, however.

Space constancy

None of our subjects reported any apparent perceptual instability of the fixated target during sustained deviation of the covered eye. The tests run in 1 subject and designed to study that particular aspect also failed to disclose any motion of the fixating eye (as monitored by an infrared corneal reflection device), such as a slow drift in the direction of the applied deviation under both sustained deviation or during transient pulling. This subject did not perceive any target motion during transient deviations. These observations confirm the general idea that no reflex connections exist between the two eyes, as evidenced in darkness by Ilg *et al.* (1989). Since, in our experiments, mechanical deviation of the covered eye did not affect the fixating eye, and since no reflex seems to reciprocally affect the posture of the eyes, space constancy was fully preserved. This confirms that our attempt to modify proprioception alone was successful, and that unlike the eye-press procedure (Stark and Bridgeman, 1983) the scleral lens technique that we developed to move the covered eye does not affect muscle activation in the fixating eye.

Eye position sensing

It is generally recognized that eye position is not consciously sensed (Merton, 1964); only extremely well trained subjects may be able to perceive with any accuracy the resting position of the eyes (Skavenski and Steinman, 1970; Skavenski, 1972). It follows

that the mislocation of targets and the shift in perceived straight ahead is not to be related to consciousness of eye position. Besides, the subject's cornea was made insensitive by local anaesthetic. Nevertheless, changes in object localization occurred, demonstrating that the signals altered by the eye-pull procedure, although not reaching consciousness, had a definite effect on sensorimotor control of the eyes and particularly on target localization.

Ocular muscle proprioception and efference copy

Two models have been proposed to describe the visual location of targets. Proprioception was hypothesized by Sherrington (1918) as providing the necessary signal for accurate eye position sensing (inflow theory) from which target location is determined. This model was an alternative to the earlier proposal by Helmholtz (1867) that sensing of eye position is based on the monitoring of muscle commands—the outflow theory. A detailed discussion of the arguments in favour of afference or efference models appeared in a recent article by Mittelstaedt (1989). Over the past 20 yrs several authors dealing with strabismics, sometimes using the same techniques, have produced data in support of either the inflow or the outflow theories. Our data support a model in which both inflow and outflow signals combine to code eye-in-orbit position. In our study, dealing with the localization of a small target which was the same size or slightly smaller than the fovea, it appears that the major component of the eye-position-coding signal is derived from eye muscle activation, but in addition a significant component is of proprioceptive origin. Ocular muscle proprioception may account for 32% (0.16D for each eye, where D is the angular misalignment) of the overall information used to sense eye position.

We have discovered that passive deviation of a nonseeing (covered) eye influences the judgement of the direction of things seen by the other eye. The passive deviation imposed on the eye in our experiment must be sensed by orbital proprioceptors, probably in the extrinsic ocular muscles. Their influence on the judgement of direction disproves the pure outflow monitoring theory of visual object location (Helmholtz, 1867). It is the first published disproof of that theory to be obtained under conditions where the seeing eye can move freely. It seems likely that what happens in our experimental situation happens to some extent in almost every judgement of the direction of a thing seen, i.e., that the estimate of the rotation of the eyes in the orbit needed for such a judgement does not come wholly from outflow monitoring, but partly from it and partly from proprioceptors.

Helmholtz's original observations on passive deviation of the seeing eye, from which he argued for outflow monitoring, are not accurate enough to prove that proprioceptors do not contribute. Helmholtz doubtless knew this. He did argue that proprioceptors contribute nothing, but from a different group of observations on the effect of passive deviation on the apparent direction of after-images. Though it has some merit, Helmholtz's argument from after-images cannot be extrapolated with absolute confidence to the seeing of external objects.

Our techniques could (although with difficulty) be adapted to passive deviation of the seeing eye. It would be interesting to discover whether in the very situation where Helmholtz first proved that outflow monitoring occurs, proprioception is demonstrably also contributing.

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PERMANENT MUSCLE WEAKNESS IN FAMILIAL HYPOKALAEMIC PERIODIC PARALYSIS

CLINICAL, RADIOLOGICAL AND PATHOLOGICAL ASPECTS

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SUMMARY

Myopathy accompanying familial hypokalaemic periodic paralysis (HPP) is much less well documented than the paralytic attacks from which the disease derives its name. Eleven affected members of a large kinship with HPP were studied clinically and radiologically for the presence of myopathy. In 4 patients muscle biopsies were also performed and in 1 of them the histological findings obtained at autopsy were compared with the CT scans of various muscles. In another patient not previously biopsied, the specimens of both amputated legs were examined histologically. The age of the studied individuals ranged from 33 to 74 yrs. The 4 youngest patients showed no clinical signs of myopathy. However, in 2 of them CT scans demonstrated discrete hypodense lesions in the leg muscles, whereas in the other 2, muscle biopsies showed a vacuolar myopathy. The other 7 patients, all older than 50 yrs, presented both clinical and CT evidence of myopathy of proximal and distal muscles ranging from very mild to very severe, males being slightly more affected than females. In all 11 patients a mean CT grading was made that was based on the abnormalities found in the different muscle groups. The myopathy appeared to be unrelated to the history of paralytic attacks, but a strong correlation was found between age and mean CT grading. It was concluded that HPP is a myopathy with permanent muscle weakness of late onset in all the patients. The expression of the paralytic attacks is variable.

INTRODUCTION

Familial hypokalaemic periodic paralysis (HPP) is an autosomal dominant disease characterized by transient attacks of muscle weakness of varying duration and severity. These paralytic attacks are amply described in the literature (Engel, 1986), but less attention has been paid to the myopathy which also may occur. In particular, the extent and the prevalence of the myopathy and its relationship with previous attacks are not well known (Engel, 1986). Although Buruma and Bots (1978) denied a relationship between the myopathy and the occurrence of paralytic attacks, both earlier (Pearson, 1964) and more recent reports (Rüdel and Ricker, 1985; Griggs, 1986) favoured such a relationship. In addition to well-defined paralytic attacks, 'abortive attacks' may occur, that is, long-lasting episodes with fluctuating weakness. In contrast to the myopathy, but similar to the paralytic attacks, this weakness can be reversed by acetazolamide (Links *et al.*, 1988). Histopathologically, HPP is characterized by vacuolation of the

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muscle fibres (Engel, 1986), but little is known about the relationship between these changes and permanent muscle weakness. No radiological reports on HPP are known.

The current study focuses on myopathy in HPP and describes the clinical and radiological findings in 11 members of a large kinship with HPP living in the north-east of the Netherlands and the histological findings in 5 of them, including an autopsy and 2 leg amputation specimens.

PATIENTS AND METHODS

Patients

A survey of a large previously described kinship (Zwarts *et al.*, 1988) revealed 55 patients with HPP among the 277 members (fig. 1) in the last 5 generations. It may be assumed that additional patients were present among the family members who could not be induced to participate in the study or were dead by the time of the study. Of the 55 patients, 35 had typical attacks. In the other 20 patients a typical history of paralytic attacks could not be elicited.

Of the 45 patients still alive, 33 were studied personally by one of the authors (T.P.L.). Of these, 19 were affected, with typical attacks, and 14 had never suffered from paralytic attacks but had slight or more severe complaints of muscle weakness. In the remaining cases and in the deceased patients a clinical history was obtained from family members, which was confirmed in some cases by data from other hospitals.

The diagnosis HPP was based on a reduced muscle fibre conduction velocity (MFCV; Zwarts *et al.*, 1988), measured in a nonparalytic state. This was measured in all 33 patients studied, with or without a history of paralytic attacks. Muscle strength was evaluated by dynamometry (Ploeg *et al.*, 1984).

The criteria for inclusion in the study were (1) a reduced MFCV and (2) agreement to have CT scanning. Eleven patients with a reduced MFCV, 5 with and 6 without attacks, gave permission for CT scanning of their muscles in a nonparalytic state. These 11 form the subject of this report and a summary of their clinical features is given in Table 1.

Representative case histories

The case numbers correspond to the numbers in fig. 1 and Table 1.

Case 1. An otherwise healthy, 33-yr-old woman had experienced fatigue and muscle pain since her thirteenth year, which curtailed her activities by the end of the day. Her symptoms were exacerbated by her menses and exercise and had steadily increased over the years. She felt that her muscle strength had decreased, but she had not experienced paralytic attacks. Neurological examination revealed no abnormalities except slight muscle weakness, particularly of the proximal limb muscles. Routine electromyographic (EMG) examination demonstrated mainly neuropathic changes. Concentric needle examination of several muscles showed some spontaneous activity (fibrillations and positive sharp waves). The motor unit action potentials were mostly normal, although some were of a slightly increased duration. She improved subjectively with acetazolamide treatment (125 mg 3 times daily) and her strength returned to normal as measured by dynamometry.

Case 3. This 35-yr-old man had had daily paralytic attacks since his thirteenth year. Initially he became totally paralysed during these attacks for 10–16 h, but by using potassium salts (10–15 g daily) the attacks were limited to slight weakness of the legs each morning. Once a month he suffered from moderate or severe weakness in the morning, despite the use of potassium salts, lasting 10–16 h. When he was aged 23 yrs old he was evaluated clinically and provocation with intravenously administered glucose caused a tetraplegia during which the serum potassium concentration decreased to 1.7 mmol/l.

Three years ago he started taking acetazolamide (125 mg 3 times daily). The paralytic attacks disappeared and his requirement for potassium salts was reduced to 2–3 g daily. He also noticed an increase of his strength between attacks, which was confirmed with dynamometry. When not taking acetazolamide, routine neurological examination revealed no abnormalities except moderate muscle weakness, particularly of the proximal muscles of his legs measured with dynamometry.

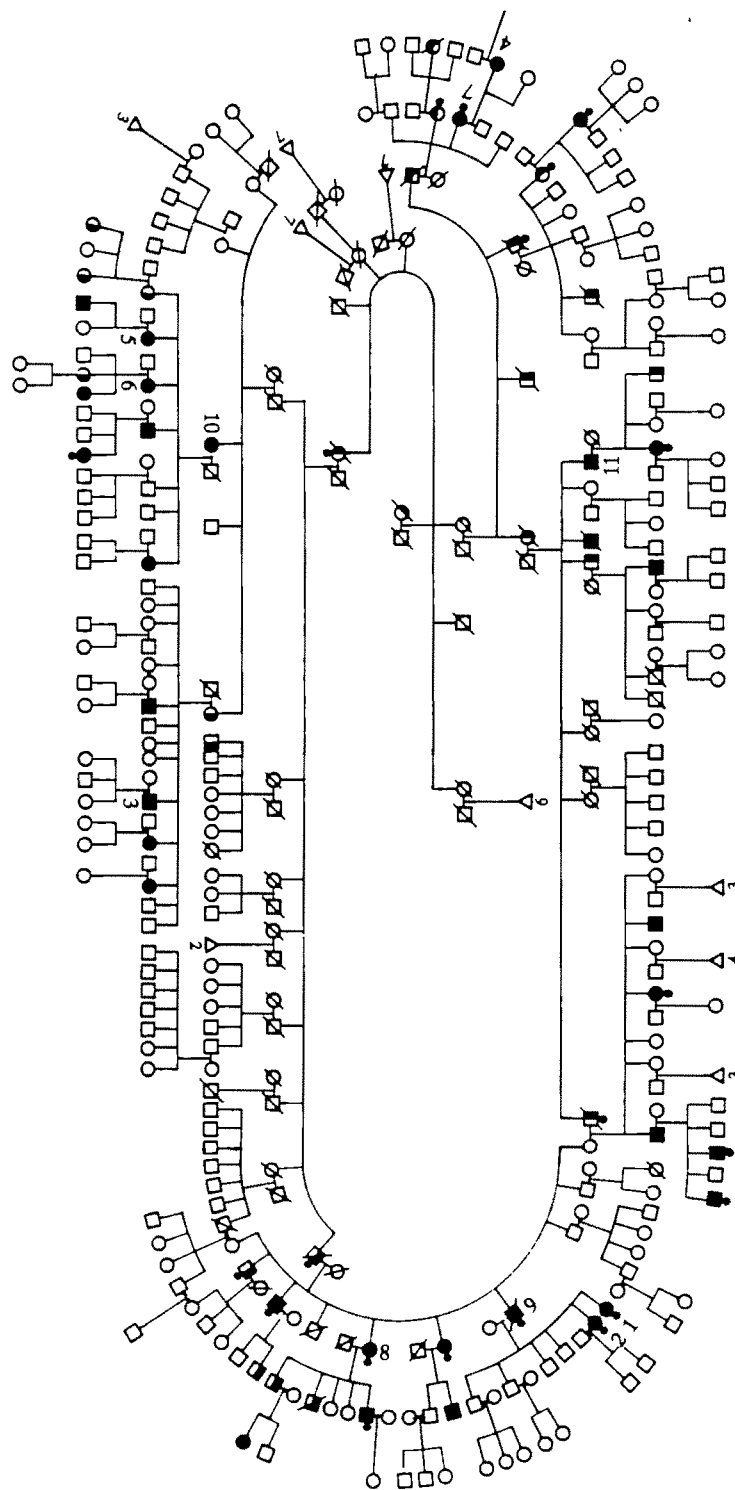


FIG. 1. Pedigree of the family with periodic paralysis. The numbers 1-11 correspond to the patients described in this article. $\square$ = males, $\circ$ = females, $\blacksquare$ = personally studied, affected, $\blacksquare$ = not studied, reported affected, $\bullet$ = affected, no attacks, only myopathic changes; $\square$ = dead, $\triangle$ = number of children, nothing known about them.

TABLE 1 CLINICAL DATA

Case	Sex/age (yrs)	Paralytic attacks. Age at onset/ at termination (yrs)	Frequency of attacks at onset/at present		MFCV (m s ⁻¹)	Muscle weakness	Serum CK myogl. (µg/l)	
1	F/33	—	—	—	3.5	Fluctuating	92	210
2	F/34	—	—	—	3.0	Fluctuating	57	120
3	M/35	13/34*	Daily	0	3.3	Fluctuating	143	410
4	F/39	17/30**	1/mo	0	3.3	Fluctuating	102	120
5	F/53	15/38	1-2/mo.	0	3.5	Slight proximal weakness legs	50	170
6	F/50	18/45	1-2/mo.	0	3.0	Slight proximal weakness legs	76	130
7	F/64	—	—	—	3.4	Slight proximal weakness legs	86	100
8	F/74	—	—	—	3.5	Severe problems with walking		440
9	M/70	—	—	—	3.6	Severely disabled	88	320
10	F/74	18/52	Weekly	0	3.7	Severe problems with walking	68	180
11	M/74	17/***	1/mo	1-2/yr	—	Severely disabled	132	

CK = creatinine kinase (normal: 0-50 µg/l), myogl = myoglobin (normal: 10-100 µg/l); MFCV = muscle fibre conduction velocity (normal: 3.9-5.3 m·s⁻¹); — = absent; * On starting acetazolamide; ** Attacks reduced by potassium; *** Attacks persist

Case 6. This 50-yr-old woman had suffered from paralytic attacks from the age of 18 to 45 yrs. The attacks occurred once or twice monthly and responded to potassium salts in varying doses (2-4 g). She had no more attacks after the age of 45, but she still noticed stiffness of the thighs after rest and on cold days. She also complained of fluctuations of her strength and of a permanent decrease in strength in her legs. Neurological examination revealed very slight weakness of the proximal muscles of the lower limbs. Treatment for 2 months with acetazolamide (125 mg 3 times daily) did not alter her symptoms and did not improve the muscle strength in her legs significantly.

The patient's daughter has been hospitalized on several occasions with paralytic attacks and a serum potassium of 1.8-2.0 mmol/l.

Case 7. This 64-yr-old woman was healthy until the age of 60 yrs, when she first experienced stiffness and muscle pains in her thighs on cold days and after sitting. She also noticed difficulty in going up and down stairs and in rising from a chair, while her arms also became weaker. These symptoms progressed slowly. Neurological examination revealed weakness of the proximal muscles of both the upper and the lower limbs. Acetazolamide (125 mg 3 times daily) partly reduced her symptoms and improved her strength, as verified by dynamometry.

Case 9. A 70-yr-old man had had diabetes mellitus since the age of 20 yrs. From the age of 55 he had noticed slowly progressive painless weakness of his legs. He had been wheelchair-bound for 4 yrs. His neurologist made a diagnosis of diabetic amyotrophy. The patient noticed that the strength of his arms

was also declining. He had never had paralytic attacks and there was no history of sudden exacerbations of the weakness associated with pain.

Neurological examination revealed severe weakness of all proximal and distal muscles, slight distal sensory impairment in the arms and legs and absent tendon reflexes. On EMG there was a mixture of neuropathic and myogenic changes in the motor unit action potentials. Nerve conduction studies were compatible with a mild diabetic polyneuropathy. Therapy with acetazolamide (125 mg 3 times daily), for 4 wks, produced no benefit.

Soon after discharge the patient died from an unrelated disease. An autopsy was performed (*see below*).

Case 11. A 74-yr-old man had had monthly paralytic attacks from the age of 17 yrs. During these attacks he had become totally paralysed for 1–3 days. After 10 yrs he had started using potassium salts in varying dosages (3–10 g) and frequency, which shortened the attacks to a maximum of 24 h. Although the frequency and the severity of these attacks had decreased with age, they had not ceased. Permanent muscle weakness developed in his 57th year, which made him wheelchair-bound over the next 10 yrs.

Neurological examination revealed tendon areflexia and severe weakness of all proximal muscles of the upper and lower limbs and the distal muscles of the lower extremities. Electromyography demonstrated a mixture of neuropathic and myogenic changes in the motor unit action potentials. One year after this investigation the patient's legs were amputated above the knees, because of ischaemic pain due to vascular insufficiency. At present the strength in his arms is still decreasing.

Serum studies

Fourteen patients were observed during attacks and serum potassium levels varied between 1.2 and 2 mmol/l. Of the 11 patients who form the subject of this report, blood samples were taken to measure the serum potassium and myoglobin concentrations and creatine kinase activity at the time of a routine visit to the hospital in a nonparalytic state. Patients were requested to avoid physical exercise on the day of the visit.

Surface electromyography

Muscle fibre conduction velocity (MFCV) was measured with 2 bipolar surface EMG electrodes placed parallel to direction of the fibres of the biceps brachii muscle between the motor point and the distal tendon. Average MFCV was estimated from the delay of the signals derived from the 2 electrodes using the cross correlation method (for details of the methods, *see* Zwarts *et al.*, 1988). For controls, MFCV is 3.9–5.3 m·s⁻¹.

Radiology

A series of CT sections was performed at predetermined levels in the neck, upper thorax, abdomen, pelvis, thigh and lower leg, according to the protocol described by Bulcke and Baert (1982). For every muscle group the CT abnormalities were graded by one of us (J.T.W.) without knowledge of the clinical picture. The classification was made according to the extent of hypodense lesions in the muscle tissue, indicating replacement of muscle by fat, and not by CT density measurements, which have already proved to be no more reliable than a qualitative assessment (De Visser and Verbeeten, 1985). Criteria for scoring were (fig. 2):

- 0 = normal;
- 1 = minimal abnormality; small hypodense areas within the muscle;
- 2 = clear abnormality; replacement of areas of muscle tissue by fat, but less than 50%;
- 3 = severe abnormality; replacement of more than 50% of area of muscle tissue by fat;
- 4 = end stage; total or subtotal replacement of muscle tissue of fat.

Morphological studies

Open muscle biopsies in Cases 1, 2 and 5 were performed on the vastus medialis muscle and in Case 9 on the right biceps brachii muscle. At autopsy in Case 9 care was taken to sample the muscles at the levels scanned by CT. The same was done with the amputated legs of Case 11. All material was embedded in paraffin and stained with haematoxylin-eosin and PAS stains. The percentage of vacuolated fibres in the biopsies was estimated by counting the vacuolated fibres among at least 100 cross-sectioned fibres. In addition, the muscle biopsies from Cases 1, 2 and 9 were snap-frozen for histochemical studies, including

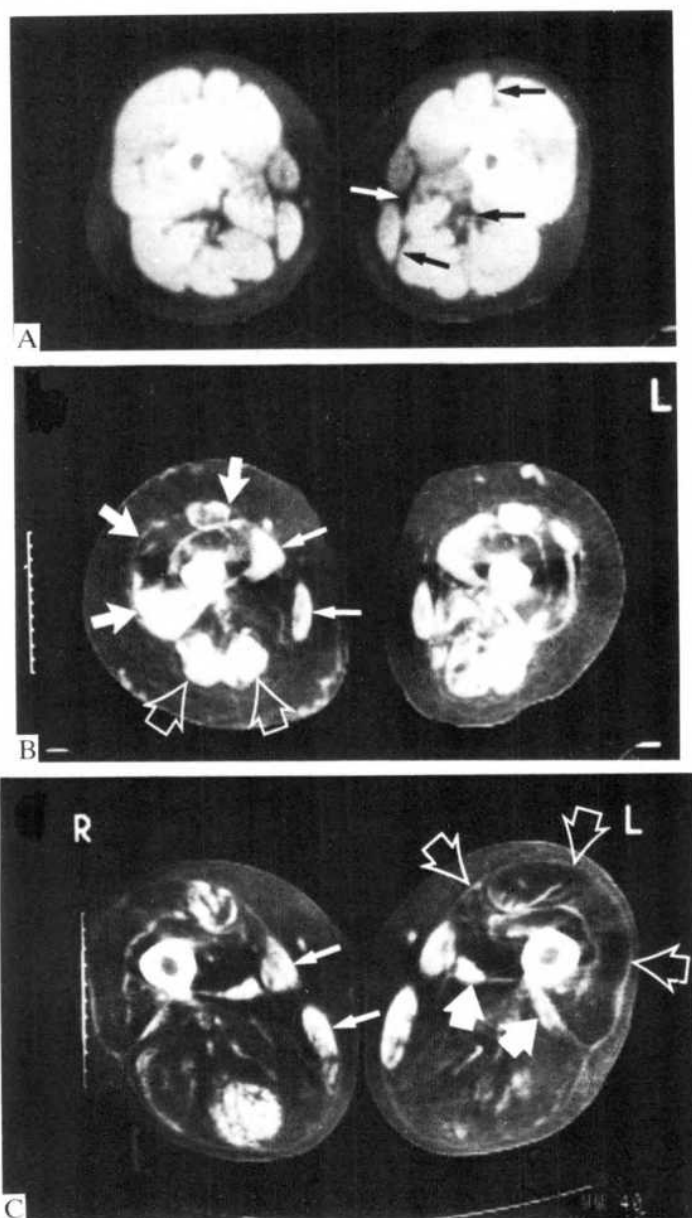


FIG. 2. Examples of various grades of muscle involvement in CT scans. A, *Case 2*. Normal appearances without signs of replacement of muscle tissue by fat (grade 0). Normal fat planes and areas between muscle groups indicated by arrows. B, *Case 8*. Minimal involvement of sartorius and gracilis (small arrows, grade 1). Involvement of more than 50% in quadriceps (large arrows, grade 3). Posterior groups show approximately 50% involvement (open arrows). Note some differences in severity between left and right; this impedes completely accurate and reproducible rating. C, *Case 10*. Clear involvement of sartorius and gracilis muscles but less than 50% affected (small arrows, grade 2). Severe involvement of more than 50% in posterior groups (grade 3), subtotal: only central areas at left are spared (large arrows). Virtually total involvement of quadriceps at left (open arrows, grade 4).

adenosine-triphosphatase (ATPase) reactions at pH 9.4, 4.6 and 4.3, NADH-tetrazolium reductase reaction, succinate dehydrogenase reaction and PAS stains with and without diastase pretreatment, Oil red O, sudan black B and Gomori trichrome stains. Four samples from each of the same 3 muscle biopsies were studied by electron microscopy.

For each biopsy the pathological characteristics were graded on a 5 point scale by one of us (W.M.M.; fig. 3):

- 0 = normal muscle tissue;
- 1 = vacuolation typical for HPP, slight fibrotic changes and replacement by fat;
- 2 = vacuolation, extensive fibrotic changes and/or replacement by fat;
- 3 = almost total replacement by fat, sporadic muscle tissue;
- 4 = no recognizable muscle tissue but assumed to be muscle tissue in view of the macroscopical appearance and localization.

RESULTS

Clinical profile

The age of the 11 patients was 33–74 yrs. The frequency of paralytic attacks ranged from none to daily. Permanent muscle weakness (PMW) was present in the 7 oldest patients (Table 1). The 4 youngest patients complained of fluctuating weakness and fatigue of the legs. The patients in the fifth and sixth decades suffered mainly from weakness of the thighs, first detected during stair climbing and rising from a chair. All patients over 70 yrs old were severely disabled, especially the 2 males. The 2 female patients were still able to walk with assistance.

Case 8 was thought to be disabled from bilateral hip arthrosis and Case 9 was diagnosed as diabetic amyotrophy. Case 11 had vascular insufficiency in both his legs.

The muscle weakness in the patients with PMW was symmetric with a predominance in the leg muscles. It was accompanied by tendon areflexia, but not by visible atrophy. The proximal and distal muscle groups were equally affected. Serum potassium levels between attacks were normal. Serum creatine kinase ranged from 50–143 (normal 0–50) $\mu\text{g/l}$ and serum myoglobin from 100–440 (normal 10–100) $\mu\text{g/l}$ (Table 1).

Radiological findings

Grading of the CT scans of all patients (Table 2) revealed that the muscles of leg and pelvic girdle were more affected than the arm and shoulder girdle muscles and some distal leg muscles were affected to the same extent as the proximal muscles. Fig. 4 shows a full CT study of a representative patient (Case 7). The earliest visible abnormality appears to be a small hypodense lesion in the centre of the muscle, whereas in later stages there is more extensive replacement of the central muscle tissue by fat. At the end stage only a thickened fascia seems to be visible (*see also* fig. 2). For all patients the sum of the CT stages of 18 muscle groups was related to age (fig. 5). It was found that the score of the patients with a history of paralytic attacks was not clearly different from the patients without attacks, but that there was a correlation with age. The Spearman rank correlation for age was 0.94 ($z = 3.00$, $P < 0.005$).

Morphological findings

The open muscle biopsies of the 4 cases (1, 2, 5, 9) all revealed the characteristic vacuoles in muscle fibres. Some of the vacuoles contained PAS-positive granular material. In Case 5 approximately 10% of the fibres possessed vacuoles, in Case 2 approximately 15% and in Cases 1 and 9 approximately 20%. All biopsies were classified as stage 1.

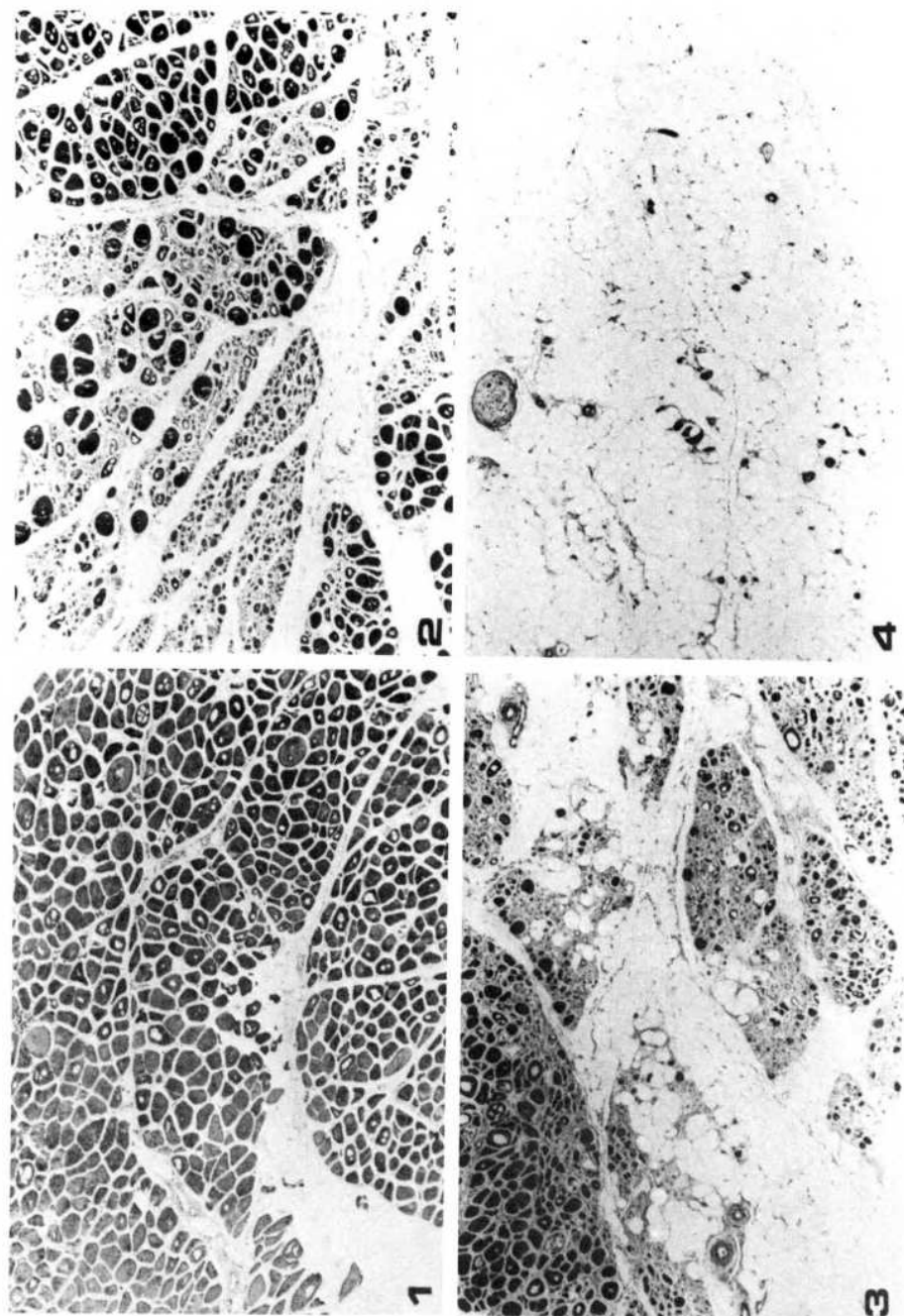


FIG. 3. Histological stages 1-4, obtained at autopsy in *Case 9* (for definitions of the stages, see text), haematoxylin-eosin, $\times 35$. (1) Left peroneus muscle, stage 1: many vacuolated fibres and increased variability in fibre size, but no substantial fibrosis or increase in fat; (2) left biceps brachii, stage 2: vacuolated fibres, atrophic fibres and focal fibrosis; (3) right gastrocnemius, stage 3: vacuolated fibres, atrophic fibres, advanced fibrosis and increase in fat; (4) right soleus muscle, stage 4: complete replacement of muscle by adipose tissue.

TABLE 2. GRADING OF CT SCANS*

Age (yrs)	Case											Total
	1 33	2 34	3 35	4 39	5 53	6 50	7 64	8 74	9 70	10 74	11 74	
<i>Level</i>												
Neck												
Ventral group	0	0	0	0	0	0	0	0	0	0	0	0
Dorsal group	0	0	0	0	0	1	1	1	1	2	2	8
Thorax												
Pectoral group	0	0	0	0	0	0	0	0	0	0	x	0
Periscapular group	0	0	0	0	0	0	0	0	0	0	x	0
Paraspinal group	0	0	0	1	1	1	1	1	1	2	1	9
Perihumoral group	0	0	0	0	0	0	1	1	1	1	2	6
Abdomen												
Abdominal wall	0	0	0	1	0	1	1	1	1	2	1	8
Paraspinal group	0	0	0	0	1	0	2	1	3	2	4	13
Psoas group	0	0	0	1	1	1	2	2	2	4	3	16
Pelvis												
Abdominal wall	0	0	0	1	0	0	1	1	1	2	1	7
Iliopsoas group	0	0	0	0	1	1	1	2	3	4	4	16
Gluteus group	0	0	1	0	1	1	2	2	4	3	4	18
Thigh												
Quadriceps group	0	0	0	1	0	1	2	3	3	4	4	18
Sartorius, gracilis	0	0	0	1	0	0	1	1	1	2	3	9
Posterior group	0	0	1	1	1	1	2	2	4	3	4	19
Lower legs												
Anterior group	0	0	0	0	0	0	1	2	1	2	3	9
Deep posterior group	0	0	1	1	0	1	2	2	3	4	3	17
Superficial group	0	0	0	0	1	2	4	4	3	4	4	22
Total	0	0	3	8	7	11	24	26	32	41	43	

* Criteria for scoring 0-4 (see text). x = classification not possible.

An increased variability in fibre size and an increased number of central nuclei were also observed, especially in Case 9, in whom pathological changes were most advanced. In the ATPase reactions in Cases 1, 2 and 9 both type 1 and 2 fibres were found to be affected; type-grouping was not observed. The Gomori trichrome stain revealed 4 fibres with bright red deposits in Case 9 (fig. 6A), 1 such fibre in Case 2 and none in Case 1. With the NADH tetrazolium reductase reaction intense focal reactivity was observed in several fibres in Case 9 (fig. 6B), but not in Cases 1 and 2. Ultrastructurally, some tubular aggregates were found in Cases 1 and 2 (fig. 6C), but not in Case 9. Taken together, the enzyme histochemical and ultrastructural findings indicate that tubular aggregates were present in all 3 patients, but to a very limited extent. Vacuoles, partly surrounded by membranes, were readily observed in all 3 biopsies that were studied electron microscopically (fig. 6D).

The autopsy of Case 9 showed the characteristic vacuoles in all skeletal muscle samples (fig. 3). In addition, many atrophic fibres were observed scattered throughout the fibre bundles and not grouped together. The more affected muscles displayed extensive fibrosis and an increase in fat (fig. 3; see next paragraph). The diaphragm and intercostal muscles also showed vacuoles. Light microscopy of the heart revealed no abnormalities; electron microscopy was not performed. Smooth muscle and peripheral nerves were not examined.

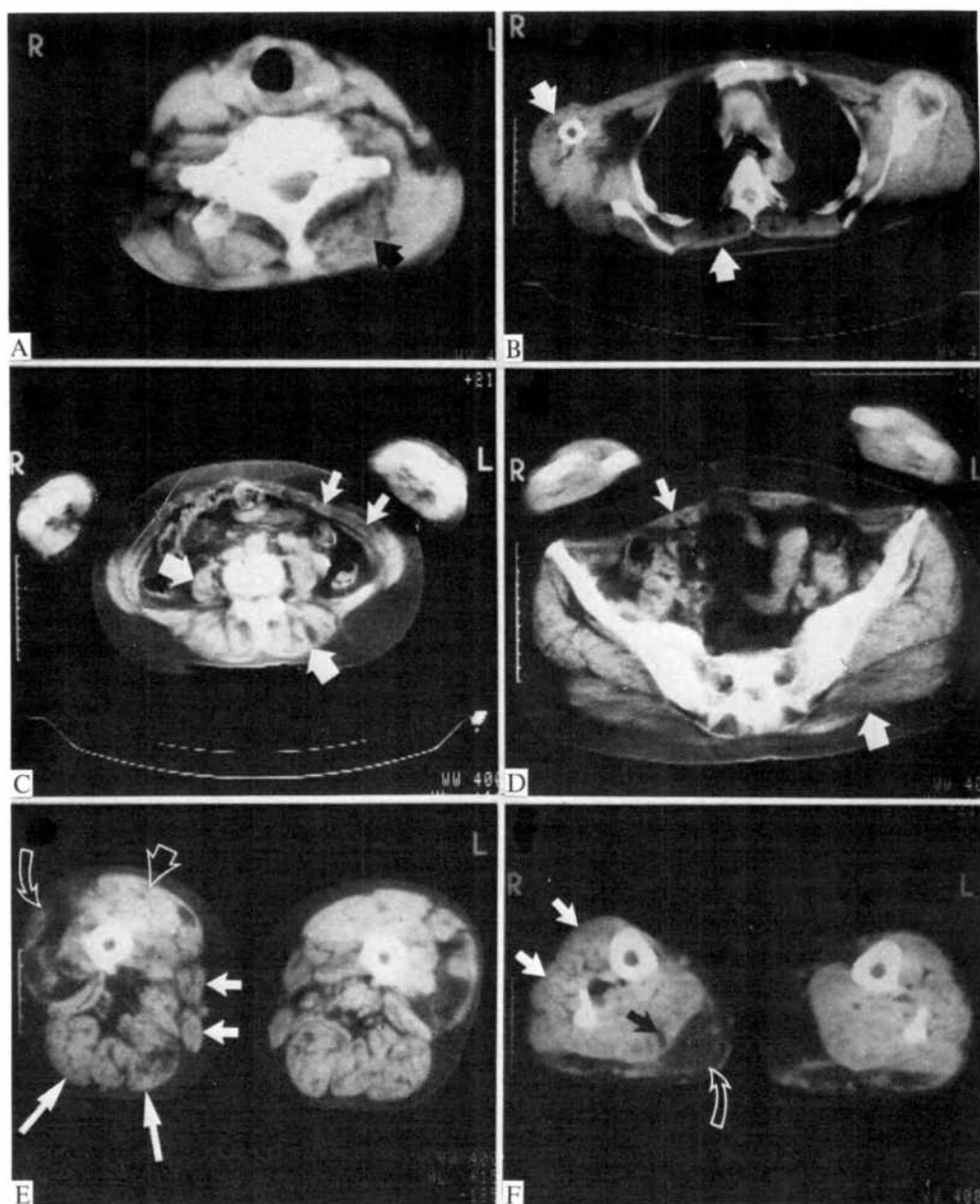


FIG. 4. Full CT study of a representative patient (Case 7). A, neck: normal appearances of ventral muscles, grade 1 involvement of dorsal paraspinal group (arrow). B, thorax: normal appearances for pectoral and periscapular muscles, grade 1 involvement of paraspinal and perihumeral groups (arrows). C, abdomen: grade 1 involvement of abdominal wall muscles (arrows), grade 2 of iliopsoas and paraspinal groups (large arrows). D, pelvis: grade 1 involvement of superficial abdominal muscles (arrow), grade 2 of iliopsoas and gluteal groups (large arrow). E, thigh: grade 1 involvement of sartorius and gracilis (arrows), grade 2 involvement of the quadriceps group as a whole, but rather uneven distribution with more severe involvement in lateral areas (curved arrow), minimal involvement anterior leg (open arrow); more diffuse grade 2 involvement of posterior groups (large arrows). F, lower legs: grade 1 involvement in anterior groups (arrows), grade 2 in deep posterior groups (black arrow), grade 4 in superficial groups (curved arrow).

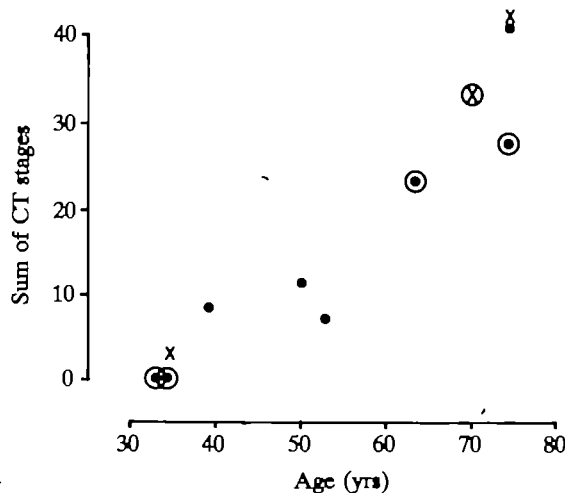


FIG. 5. Sum of CT stages of 18 muscle groups, related to age (Spearman rank correlation 0.94, $z = 3.00$, $P < 0.005$). X = male, closed circle = female; open circle = no attacks.

Comparison between CT scan appearances and histology

In Cases 9 and 11 the CT appearances could be compared with the histological findings in the autopsy and in the amputation specimens of the legs, respectively. In Case 9, muscle samples from the different muscle groups were taken at the levels of the CT scans. There appeared to be a striking relation between CT grading and the histological grading (fig. 7). All stages were found in the proximal as well as in the distal legs. There was no preference for the higher stages in the proximal muscles. In Case 11 virtually all muscle tissue was replaced by fat, but the macroscopic features of muscle bundles were still apparent (fig. 8). The only visible muscle tissue was found just below the fascia, which presumably explains the CT finding of a 'thickened fascia'.

DISCUSSION

Hypokalaemic periodic paralysis is transmitted as an autosomal dominant condition. In women the disease tends to be less severe than in man (Engel, 1986). Sometimes patients develop only a single attack or escape manifest attacks. The variable expression of the attacks has led to a denial by some individuals of being affected and has given the impression that the gene can 'skip' generations.

Permanent muscle weakness (PMW) in HPP is a well-known phenomenon (Biemond and Polak Daniels, 1934; Dyken *et al.*, 1969), but the causal relationship between the periodic paralytic attacks and the myopathy has been a source of debate. Pearson (1964), for example, stated that PMW does not appear until at least 5 yrs after the onset of the attacks and he was supported recently by Rüdél and Ricker (1985) and Griggs (1986). Buruma and Bots (1978), on the other hand, presented a patient in a Dutch family with HPP, probably unrelated to our family, in whom muscle weakness and vacuolar changes were found. This patient has remained free of attacks until the present (personal

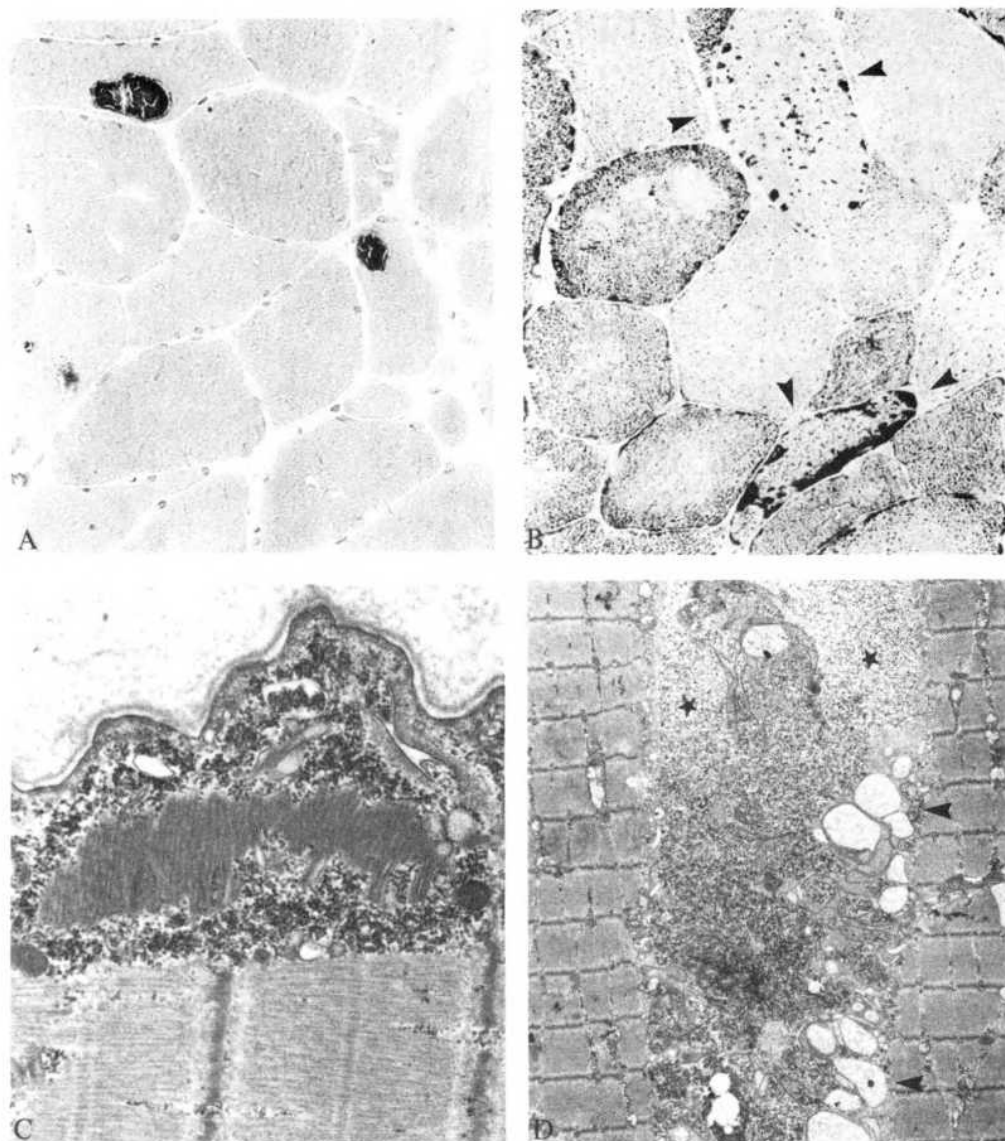


FIG. 6. A, bright red deposits in the Gomori trichrome stain in the biopsy of *Case 9* ($\times 224$). B, NADH tetrazolium reductase reaction showing dense deposits (arrowheads) in the same biopsy as in A ($\times 224$). C, electron micrograph of *Case 1* showing subsarcolemmal tubular aggregates ($\times 21,043$). D, electron micrograph of *Case 1* showing several small membrane-bound vacuoles (arrowheads) and granular deposits (asterisks) with membranes presumably derived from a ruptured vacuole ($\times 4685$).

communication). Later, it was reported that all his sibs with HPP, diagnosed by the occurrence of paralytic attacks, suffered from PMW (Buruma *et al.*, 1985). In the present family, PMW without periodic paralytic attacks occurred in 40% of cases. This contrasts sharply with the findings of Johnsen (1981), who reported PMW in only 14 of the 106

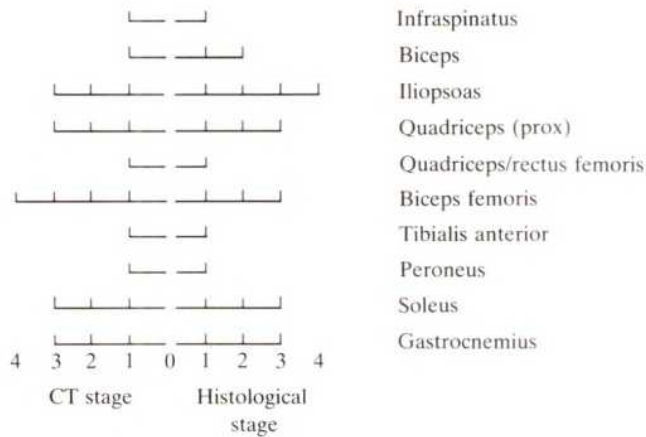


FIG. 7. Relationship between the CT stages and the pathological stages of the various muscle of Case 9, autopsied 1 yr after obtaining the CT scan.

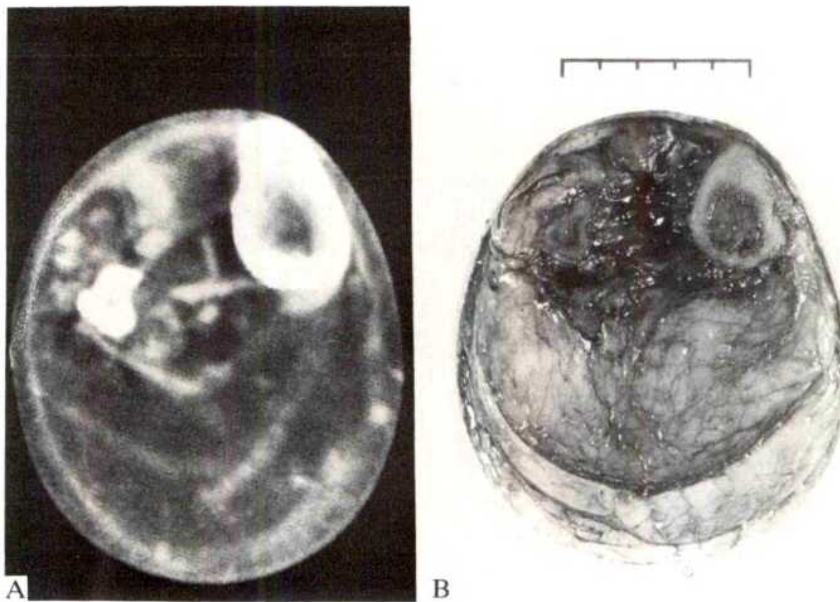


FIG. 8. A, CT section through right lower leg demonstrating extensive involvement of all muscle groups (Case 11). B, anatomical section of the same level in the same patient confirming disappearance of muscle tissue and replacement by fat.

patients with HPP from 12 families. This difference can largely be explained by our use of surface EMG measurement of MFCV, a new noninvasive method to diagnose HPP (Zwarts *et al.*, 1988). In general, needle EMG findings were not specific and neuropathic and myopathic changes could be found, as also previously described by us and by others (Kreindler *et al.*, 1964; Zwarts *et al.*, 1988). However, the surface

EMG measurement of the MFCV made it possible to include patients without paralytic attacks, and even without clinical signs of myopathy. In all patients in whom myopathic changes were found on the CT scan and/or on histological examination, MFCV was reduced. Further, PMW is probably only reported in the most serious cases, whereas cases without attacks tend to go undiagnosed, despite a positive family history of HPP.

As may be expected in the older patient population some of the patients also suffered from other illnesses, and the muscle weakness was attributed to their diseases, such as diabetes mellitus in Case 9 and vascular insufficiency in Case 11. It cannot be excluded that these concurrent diseases contributed to the muscle pathology. However, although both patients had other diagnoses in addition to their HPP, the histological changes were similar. In Case 9 the muscle biopsy and especially the samples taken at autopsy showed extensive histological changes, i.e., widespread vacuolation, atrophic fibres, fibrosis, increase of the number of internal nuclei and increase in fat. Among these changes the vacuoles are characteristic for HPP and the other changes have also been described in HPP (Tomé, 1982), and also in neurogenic disorders. However, the atrophic fibres were scattered throughout the fibre bundles and not grouped, a pattern more compatible with HPP than with neurogenic changes. The EMG studies revealed a mixture of neuropathic and myopathic changes, which was also seen in other patients with HPP without concurrent disease (Kreindler *et al.*, 1964; Zwarts *et al.*, 1988). Moreover, in Case 9, nerve conduction studies indicated only a mild neuropathy, whereas the muscle pathology was severe. Finally, no grossly visible atrophy was present. In Case 11 virtually no muscle fibres remained in many of the muscles of the amputation specimen and those that were present showed many vacuoles. These changes can hardly be attributed to vascular insufficiency alone. It remains to be seen whether a myopathy without attacks is a finding peculiar to the current family or a general feature of HPP, which is as yet underdiagnosed. PMW appeared to be unrelated to the number and severity of paralytic attacks, since it occurred both in patients with and without attacks. It may be assumed that the various clinical features, i.e. the less than average strength, occurring in patients with and without attacks, the interictal muscle weakness and the periodic paralysis only occurring in patients with attacks (Links *et al.*, 1988) can all be explained by the same structural muscle defects (*see below*). The finding of a strong correlation between PMW and age may be explained by a progressive destruction of muscle tissue. This destruction seems to continue into old age.

Measuring muscle enzymes alone is not a sensitive method for detecting carriers of HPP, because many other factors can cause enzyme elevation, such as previous exercise. Therefore the finding of slightly elevated muscle enzyme levels in some family members without symptoms, with a normal MFCV, normal muscle strength and a normal biopsy is a nonspecific finding on which no conclusions can be founded. This is in contrast with the opinion of Wiggers and Nørregaard Hansen (1985) who supposed that serum myoglobin and serum creatine kinase can be used to detect carriers of HPP. An alternative approach could be to measure the muscle enzymes after provocation (e.g., glucose stress, Hudson *et al.*, 1967). We are currently undertaking such studies.

In paralytic attacks the muscles of the legs and pelvic girdle are affected more and for longer than the arm and shoulder girdle muscles and patients complain more about minor attacks of the legs than in the arms. The severity of myopathic changes shown in the CT scans (Table 2) and found at autopsy (fig. 7) parallels this distribution,

irrespective of a history of attacks. It is remarkable that some muscles, for example, sartorius, gracilis and rectus femoris, were relatively spared. This is also observed in other myopathies (Bulcke and Baert, 1982, pp. 141–149), without a cogent explanation. HPP is not a typical proximal weakness, because some distal muscles as soleus and gastrocnemius were found to be affected to the same extent as the proximal leg muscles. In the present patients, no muscle atrophy in the limbs was visible or measurable. This is in contrast to the findings of Biemond and Polak Daniels (1934), who described atrophy so severe as to simulate a neurogenic disorder. On CT scanning, as well as on gross and microscopic examination of the amputation specimens and the autopsy, there appeared to be a progressive replacement of muscle by connective tissue or fat, altering the function, but not the size of the original muscle. This process, when observed in muscular dystrophies (e.g., Becker dystrophy), is reported to start at the periphery of the muscle, just deep to the fascia, and is known as the 'filling up process' (Bulcke and Baert, 1982, p. 89). In contrast, the focal replacement of muscle tissue in HPP begins at the centre of the muscle, just as the vacuoles do (*see below*; Dubowitz, 1985). Pseudohypertrophy, for instance of the calves, is not seen clinically or on the CT scans. Although it is not possible to predict a patient's mobility or degree of incapacity by studying the CT scan, the simple visual grading of the CT scans proved very useful in judging the severity of the disease in a semiquantitative manner (De Visser and Verbeeten, 1985). Especially in the 4 youngest patients, CT scanning was more sensitive than the clinical examination in demonstrating the presence of myopathy.

Histologically, vacuolation of muscle fibres is the hallmark of HPP. It has been reported that the vacuoles are predominantly located in type I fibres (Ionasescu *et al.*, 1974; Tomé, 1982), but they were found in both types by Engel (1986) as well as in the present cases. The number of vacuoles varies from muscle to muscle and may increase reversibly during attacks (Shy *et al.*, 1961; Ionasescu *et al.*, 1974).

This increase (Shy *et al.*, 1961), though sometimes absent (Resnick *et al.*, 1969) may indicate that the vacuoles are a manifestation of muscle membrane disturbance or destruction occurring during attacks. The reduction in MFCV is possibly caused by the membrane disability that underlies HPP. Some hypotheses have been proposed to explain the membrane disability, such as an increased conductance of the muscle membrane to sodium, a decreased conductance to potassium or an increased activity of the Na^+K^+ pump. As early as 1970, Hofmann and Smith hypothesized an increased sodium conductance. Layzer (1982) defended a decreased conduction of potassium by analysing the membrane potentials and ion concentrations between and during paralytic attacks. Hofmann (1982) opposed the theories of Layzer. Rüdel *et al.* (1984a) shared the opinion of an increased sodium conductance and a reduced excitability based on membrane voltage clamp experiments and excitability tests. More recent, Rüdel *et al.* (1984b) suggested an increased activity of the Na^+K^+ pump. This latter theory has been considered to be wrong on theoretical grounds by Martin and Levinson (1985). However, none of these theories has convincingly explained the pathophysiology of HPP.

As already mentioned, the reduced MFCV can be the expression of the membrane disability. In this respect, it is of interest that both vacuoles and a reduced MFCV found in all the currently reported cases, suggest that the membrane defect is present without manifest attacks. It is likely that membrane disturbance is present in all striated muscles, but it is unclear why some muscles are affected more severely than others.

The second histopathological characteristic of HPP is the presence of tubular aggregates, which are presumably derived from the sarcoplasmic reticulum. Such structures were observed ultrastructurally in 1 of the 3 studied patients and enzyme histochemically in the other 2. They were, however, very limited in number. Since none of these 3 patients experienced from attacks, it may be wondered whether, in contrast to vacuoles, the presence of tubular aggregates correlates with the occurrence of attacks.

There is little known about the involvement of the cardiac muscle in HPP, although acute dilatation and cardiac arrhythmia during severe attacks has been described (Kramer *et al.*, 1979). In the current Case 9, light microscopy of the heart showed no abnormalities, whereas electron microscopy was not performed. To our knowledge, the only previous histological report is that by Buruma *et al.* (1981) who also described normal light microscopic as well as enzyme histochemical findings and observed no vacuoles on electron microscopy. Electron microscopically they did find rather abundant glycogen deposition between the myofibrils of some fibres and an increase in the number of mitochondria, but these findings are nonspecific and their significance is as yet unclear.

We conclude that HPP, at least in the current family, is a myopathy with permanent muscle weakness of late onset in all patients. Periodic paralytic attacks are striking, but their expression is variable. With surface EMG measurements of MFCV, which is characteristically reduced in HPP, it is possible to detect relatives who have inherited the disease. Some of them have no complaints, others are affected by fluctuating muscle weakness due to slight periodic paralytic attacks, and some are handicapped because of reduced muscle strength.

We assume that vacuolar changes, seen at a young age, are the first histological expression of destruction of muscle tissue and are unrelated to paralytic attacks. In a later stage, at an older age, muscle tissue is destroyed to such an extent that it may cause severe disability. CT scanning is a sensitive method of confirming the presence and extent of the myopathy, not only in the proximal, but also in the distal muscles, at least in the legs.

HPP can therefore be regarded as a myopathy featuring late onset destruction of proximal and distal muscles. This myopathy, as shown in this study of 11 members of a family, is unrelated to the history of paralytic attacks. Based on the numbers in the whole family studied, it is characterized by paralytic attacks in only 60% of the cases.

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SPONGIFORM ENCEPHALOPATHY TRANSMITTED EXPERIMENTALLY FROM CREUTZFELDT-JAKOB AND FAMILIAL GERSTMANN-STRÄUSSLER- SCHEINKER DISEASES

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SUMMARY

A comparison was made of the effects of experimental intracerebral inoculation into marmosets of brain homogenates from a case of Creutzfeldt-Jakob disease (CJD) and from a member of the Wo. family with cerebral amyloid and spongiform encephalopathy – the Gerstmann-Sträussler-Scheinker (GSS) syndrome. All the inoculated marmosets developed spongiform encephalopathy (SE) after incubation times of 20–23 months in the CJD group and 25–32 months in the GSS group. Subsequent passage from 1 affected animal in each group resulted in SE developing after 17 months incubation. In every animal inoculated with CJD or GSS material and in the 2 passage experiments the most severely affected region of the brain was the thalamus which in all cases was almost totally occupied by vacuoles. Other grey matter masses were less severely and less consistently affected. Vacuolation was observed in the cerebellar granule cell layer as well as in the molecular layer and the brain stem was finely vacuolated in all cases. There were only minor and inconsistent differences between the disease transmitted from CJD compared with GSS and some differences between the original transmissions and the SE caused by passaged inocula. Severe astrocytic gliosis accompanied the spongiform changes but no amyloid was identified in any of the marmosets with experimentally transmitted disease.

The pathogenesis of the spongiform change in the thalamus was studied in a series of marmosets by light and electron microscopy 3–22 months after the intracerebral inoculation of CJD or GSS homogenates and was compared with controls. Dilated irregularly-shaped cisternae and the large complex vacuoles typical of SE, present in abundance after 18 and 22 months incubation, were considered most probably to be derived from cisternae of neuronal smooth endoplasmic reticulum.

INTRODUCTION

One of the neuropathological features of Creutzfeldt-Jakob disease (CJD) is the presence of spongiform encephalopathy (SE). CJD has been transmitted experimentally to animals and also to human patients iatrogenically by a variety of routes. Indeed the transmissibility of this condition has come to be an important element in diagnosis. In recent years we have had the opportunity to study the pathology of a number of cases of progressive cerebral disease occurring in the Wo. family, the main neuropathological changes being cerebral amyloid deposition associated with spongiform encephalopathy. The name Gerstmann-Sträussler-Scheinker (GSS) has been applied to this familial type of

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neurological disease and cases in the family reported by Adam *et al.* (1982), the largest kindred of its kind so far described, varied greatly in the duration of the illness, in the distribution and severity of amyloidosis and in the intensity and distribution of spongiform changes. Recently, genetic linkage has been found between illness in this family and a missense variant in the prion gene which codes for the protein, of which an abnormal isoform accumulates during development of the disease (Hsiao *et al.*, 1989). Transmission from the brain of one member of this family to New World monkeys has been described (Rosenthal *et al.*, 1976; Masters *et al.*, 1981), this particular case having had an illness of less than 1 yr in duration and having cerebral pathology typical of CJD. It was considered of interest to determine whether a neurological disease could be transmitted from the brains of family members who had disease of much longer duration with progressive cerebellar ataxia to compare the pathology with that caused by transmission of typical sporadic spongiform CJD encephalopathy and with inoculation of brain tissue from other conditions. The progression of spongiform changes in the experimental animal was studied by light and electron microscopy.

MATERIAL AND METHODS

Animals

A total of 19 marmosets (*Callithrix jacchus*, 7 males, 12 females) aged between 11 months (adolescent) and 66 months (adult) at the start of the experiment were used. Animals were housed singly, or in pairs with another animal inoculated with tissue from the same patient and were fed a normal daily diet of bread, fruit and monkey chow. Prior to inoculation the animals were given a brief behavioural examination and their general levels of activity were assessed using automated equipment. No abnormal behaviours were detected before inoculation. After inoculation animals were observed daily and abnormalities in movement and behaviour were noted. Every 5 months all animals were examined intensively and their overall level of activity was assessed using automated equipment.

Inoculation procedure

Fresh cerebral cortical tissue was taken at necropsy from Cases 1–4 and stored at -40°C until required. Inoculum was prepared as a 10% weight/volume homogenate of tissue in 0.85% sterile saline. Animals were anaesthetized with 1.0 ml/kg alphaxalone/alphadolone (Saffan, Glaxovet) intramuscularly. A 50 μl injection of homogenate was made intracerebrally into each of 6 sites in each animal (a total of 0.3 ml). Injections were made stereotactically into the caudate nucleus, hippocampus and parietal cortex in the left hemisphere and the nucleus accumbens, amygdala and parietal cortex in the right hemisphere. Each animal was also injected intraperitoneally with 0.7 ml inoculum. All animals recovered well from the inoculations and were behaving normally within 1–2 days.

Animals were killed at the times after inoculation as indicated in the Table. In Experiments I–V animals were killed by an overdose of pentobarbitone when they were clearly affected and their physical conditions were deteriorating rapidly. Half of each brain was fixed in 10% formol saline and the other half was frozen for subsequent passage. In Experiments VI and VII animals were perfused transcardially at a controlled pressure of 120 mmHg, under deep pentobarbitone anaesthesia, with cold saline followed by cold freshly prepared 3% glutaraldehyde, 1% paraformaldehyde in 0.07 M sodium cacodylate pH 7.4. After perfusion, brains were removed rapidly, cut coronally into blocks and postfixed in the same fixative.

Details of the animals used, the inocula injected intracerebrally, survival times and clinical status of the animals in the various experiments are given in the Table.

Source of inoculum

Case 1. A.W., female, died aged 71 yrs. Unsteadiness of gait and vertigo progressed to spasticity and rapidly deteriorating global dementia. Occasional myoclonic jerks were observed and EEG showed periodic complexes typical of CJD shortly before death which occurred after an illness of 8 wks' duration. There

TABLE SOURCE OF INOCULUM, SURVIVAL TIME AND CLINICAL STATUS OF MARMOSETS GIVEN INTRACEREBRAL INOCULATIONS OF BRAIN HOMOGENATES

Experiment	Animal	Inoculum	Survival time (mos)	Neurological status	Duration of clinical illness
I	1	Case 1 (CJD)	20	Severe*	2 mos
	2	Case 1 (CJD)	20	Severe	3 mos
	3	Case 1 (CJD)	22	Acute	1 day
	4	Case 1 (CJD)	23	Severe	3 wks
II	5	Passage from 3	17	Severe (including tremor)	5 mos
III	6	Case 2 (GSS)	25	Severe	12 mos
	7	Case 2 (GSS)	29	Severe	2 wks
	8	Case 2 (GSS)	32	Acute	2 days
	9	Case 2 (GSS)	32	Severe	1 mo
IV	10	Passage from 8	17	Severe	5 mos
V	11	Case 3 (Alzheimer's)	10	Non-neurological intercurrent illness	—
VI	12	Case 4 (normal)	10	Well	—
	13	Case 4 (normal)	3	Well	—
VII	14	Case 1 (CJD)	3	Well	—
	15	Case 2 (GSS)	3	Well	—
	16	Case 1 (CJD)	8	Well	—
	17	Case 1 (CJD)	13	Mild (eating off floor)	1 wk
	18	Case 1 (CJD)	18	Prodromal (very quiet)	—
	19	Case 1 (CJD)	22	Severe	9 mos

* Severe = ataxia, broad-based gait, daytime somnolence, salivation, eating off floor.

was no relevant family history. Postmortem examination (Dr F. R. Wells) showed atrophy of frontal and temporal gyri and on histological examination there was severe widespread spongiform change in the cortex accompanied by marked astrocytic hyperplasia and neuronal loss. In silver-impregnated sections there were no senile plaques or neurofibrillary tangles and no amyloid plaques or amyloid angiopathy were identified with Congo red staining. The appearances were characteristic of CJD.

Case 2. J.C., female, died aged 46 yrs (Case 4 of the Wo. family described by Adam *et al.*, 1982). Her illness began with ataxia, slurring of speech and clumsiness of fine movements of the hands. These progressed steadily and she became bedridden and doubly incontinent within 5 yrs. Progressive deterioration of memory and other cognitive functions developed late in the disease until a decorticate state was reached a few months before death which occurred after an illness of 6 yrs. Postmortem examination of the brain showed generalized atrophy and histological examination showed severe widespread spongiform changes, neuronal loss, astrocytic hyperplasia and marked deposition of amyloid in the form of droplets and 'kuru type plaques' in the cerebral and, particularly, in the cerebellar cortex. There was no amyloid angiopathy and no evidence of Alzheimer's disease. The combination of cerebral amyloid and spongiform encephalopathy indicated a diagnosis of GSS.

Case 3. A. C., male, died aged 56 yrs after an illness of 6 yrs characterized by progressive dementia. Postmortem examination (Dr C. J. Bruton) showed severe cortical atrophy. There were massive numbers of senile plaques and neurofibrillary tangles typical of Alzheimer's disease.

Case 4. A.H., male, died aged 74 yrs after acute myocardial infarction. There had been no evidence of psychiatric or neurological illness and no family history of either.

Experiments

I. Marmosets 1–4 were inoculated intracerebrally with homogenate derived from the brain of Case 1. Animals were allowed to survive until there was clear evidence of neurological illness and were killed 20–23 months after the inoculation.

II. Marmoset 5. In this experiment, the inoculum was derived from one cerebral hemisphere of marmoset

3, removed and frozen at the time the remainder of the brain was fixed in formalin. The homogenate was prepared and the inoculation sites were as described above. This animal was killed after 17 months incubation when there was evidence of moderately severe neurological illness, and represents one animal passage of typical CJD.

III. Marmosets 6–9 were given intracerebral injections of homogenate prepared from the brain of Case 2. These animals were allowed to survive 25–32 months having shown signs of neurological illness ranging from several days' to several months' duration.

IV. Marmoset 10. In this experiment the inoculum was prepared by homogenizing one hemisphere of marmoset 8 and giving intracerebral injections as described. Animal 10 was killed after 17 months' incubation when it had shown neurological abnormalities for several months. This represents one animal passage of GSS.

V. Marmoset 11. This animal was given intracerebral injections of inoculum prepared from the brain of Case 3 (Alzheimer's disease) and was killed because of intercurrent illness after 10 months. There had been no sign of neurological illness. The brain of this marmoset was examined only by light microscopy of paraffin embedded tissue.

VI. Marmosets 12 and 13 were given intracerebral injections of brain tissue from Case 4 and were regarded as normal controls. They were killed 3 months and 10 months after inoculation, neither having shown evidence of any abnormality.

VII. Marmosets 14–19 were inoculated intracerebrally with brain homogenate derived from Case 1 (with the exception of 15 which received inoculum prepared from Case 2). This experiment was intended for the electron microscopic study of the progression of spongiform encephalopathy and the results of Experiments I and II had indicated that the pathology of animals inoculated with brain tissue from Cases 1 and 2 was indistinguishable. Animals of Experiment VII were killed 3, 8, 13, 18 and 22 months after inoculation. At 3 and 8 months the animals seemed normal, at 13 and 18 months there were signs of mild neurological disturbance and in the animal killed 22 months postinoculation there had been evidence of severe illness for several months.

Neuropathological methods

The brains of animals 1–12 were examined only by light microscopy of paraffin sections. Blocks were taken from many regions of cerebrum, brainstem and cerebellum, and embedded in paraffin wax. Sections were stained by haematoxylin-eosin, haematoxylin-van Gieson, luxol fast blue-cresyl violet, Congo red, silver impregnation for axons by Glee's method, and by immunoperoxidase staining for glial fibrillary acidic protein (GFAP). The brains of animals 13–19, which had been perfused with glutaraldehyde, were quickly removed and cut in the coronal plane at the level of the thalamus. Blocks of thalamus were taken for electron microscopy, postfixed in osmium tetroxide, dehydrated and embedded in Araldite. After examination of 1 μ m sections stained with toluidine blue an area of the block was selected for ultrathin sectioning. Sections were stained with uranyl acetate and lead citrate and examined in a Jeol 100 CX electron microscope at 80 kV. After thalamic blocks had been selected the remainder of the brain was immersed in formol-calcium (10% formaldehyde in 1% calcium acetate) and subsequently blocked and embedded in paraffin wax. In some cases the preliminary perfusion with glutaraldehyde made subsequent cutting and staining of paraffin sections rather unsatisfactory but in other cases it had not caused much change in the staining qualities of the sections. All the neurohistological methods mentioned above were used.

RESULTS

Behavioural observations

Signs of behavioural abnormality were observed in all marmosets in Experiments I–IV and in 3 in Experiment VII (*see* Table). A prodromal stage of some weeks' duration, during which the animals were unusually quiet and dishevelled, was followed by the appearance of more obvious neurological disturbance. Only the prodromal stage was observed in animal 18. The neurological disturbance lasted from 1 day to several months and began with a deterioration in balance such that the animal frequently wobbled on its perch but compensated for this by moving around. There followed a period in which

the marmoset could be observed to move carefully, never allowing more than one limb to leave the ground at once. This developed into a broad-based ataxic gait with exaggerated movements, e.g., the feet lifted high off the ground with each step. Animals became withdrawn and were often observed staring at the wall while failing to take an interest in events occurring within the room. An early sign consisted of eating off the floor rather than holding food in the hands. This developed into a difficulty in eating cleanly so that food debris was left clinging to the face. Excess salivation (drooling) was common. Most animals became somnolent during the daytime especially in the afternoon although data from automatic movement monitoring devices suggested that night sleep was disturbed.

Neuropathological observations

Experiments I and II (marmosets 1–5; transmission and passage of CJD)

In the cerebral cortex there was patchy vacuolation (spongiform change) varying in severity and distribution (fig. 1). In the cortex the vacuoles were anything from 5 to 15 μm in diameter, were most commonly seen in the deeper layers (3–5) and lay adjacent to neuronal nuclei, impinging on them and causing distortion. There were occasional clusters of vacuoles, like bunches of grapes, but they tended not to be coalescent or form large cavities. On the whole the frontal cortex was mildly affected, the cingular cortex posteriorly quite markedly vacuolated in all 5 animals, the hippocampal and occipital cortex generally spared or very slightly affected. In particular the calcarine cortex showed no vacuolation in any of the marmosets primarily inoculated. The most

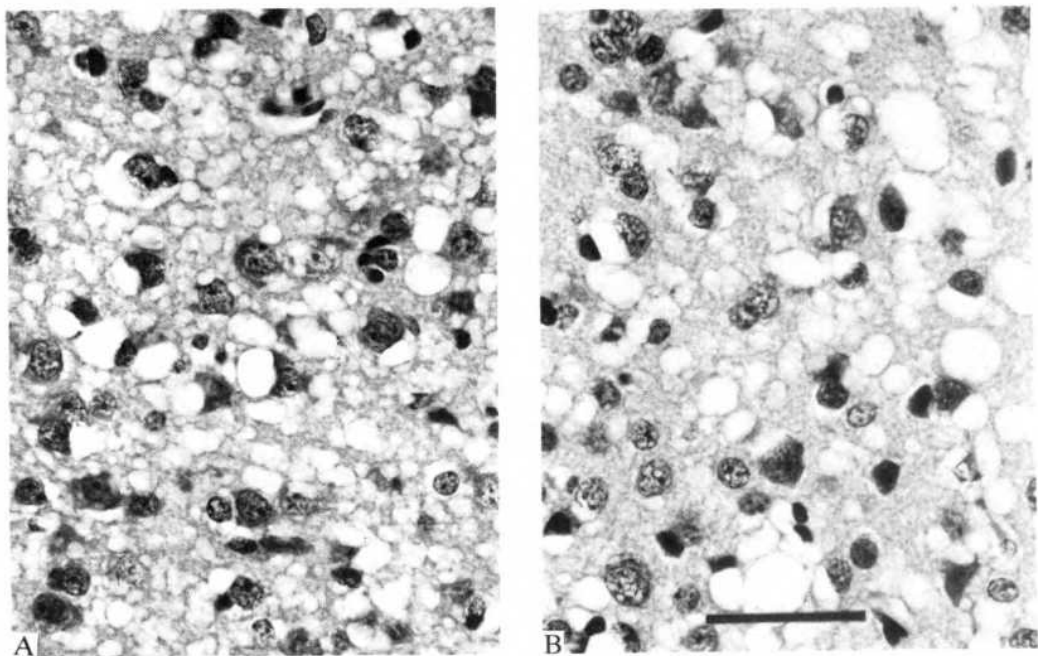


FIG. 1. Spongiform change in cortex of marmosets after primary inoculation from CJD (Case 1) and GSS (Case 2) patients. A, frontal cortex of animal 3; B, frontal cortex of animal 8. Haematoxylin-eosin. Bar = 50 μm .

striking degree of spongiform change was present in the deep grey matter of all the animals of this group, the worst affected structure being the thalamus (fig. 2). Here the vacuoles were bigger, coalescent and almost totally replaced the neuropil and blurred the identity of the nuclei. Neurons were severely distorted and were difficult to identify. Astrocytes were very numerous as they were wherever spongiform changes were apparent. Other deep grey nuclei were more variable in appearance than the thalamus. In Experiment II the pattern of vacuolation was similar to that in Experiment I with the most severe pathology in thalamus and lesser involvement of the caudate, putamen and septal region. The occipital cortex including the calcarine, however, showed a severe degree of spongiform change.

The brainstem grey matter showed spongiform changes of varying degree of severity, nowhere as severe as in the thalamus and in some instances consisting only of a diffuse scattering of small vacuoles. The cerebellum was affected to some degree in all cases, vacuoles being found in the molecular and granule cell layer as well as in Purkinje cells (fig. 3). Hyperplasia of Bergmann astrocytes and abundant isomorphous glial fibrosis of the molecular layer were present. There was little or no evidence of Purkinje cell loss, no torpedoes were present in any case, and there was no sign of amyloid.

Experiments III and IV (marmosets 6–10; transmission and passage of GSS)

The appearances of these brains were, on the whole, very similar to those of marmosets 1–5. There was, however, generally severe vacuolation of the cortex varying in degree and continuity from one animal to another, 8 and 10 showing the most severe cortical vacuolation of all the animals studied. In addition to the severe spongiform changes seen in the thalamus, there was less pathology in the basal ganglia and almost total sparing of the calcarine cortex. There was no obvious loss of myelin in the white matter of the hemispheres, cerebellum or brainstem. There was, however, an increase in the number of astrocytes and astrocytic fibrils demonstrable with GFAP antibody.

Experiments V and VI (marmosets 11–13)

These brains were examined in paraffin sections and by electron microscopy and were without apparent pathology. No spongiform changes were visible in either cortex, deep grey matter, brainstem or cerebellum. There was no difference between them in the extent and numbers of astrocytes in grey or white matter, no amyloid was demonstrable and on silver impregnation there were no neuritic plaques and no neurofibrillary tangles visible. From the point of view of comparison with the CJD or GSS-inoculated marmosets, it was felt that all these 3 marmosets (11–13) could serve as controls. In the normal animals the expected appearance of neurons and neuronal processes was observed by electron microscopy. Small rounded or oval cisternae were present in some, usually but not solely dendritic, processes (fig. 4). These were infrequent and had to be searched for. If, however, perfusion-fixation was delayed or imperfect, distended cisternae were present in abundance. In such cases there were also other signs of poor fixation, notably swollen clear mitochondria, abundant extracellular space and imperfectly preserved membranes. In all the material examined, therefore, special attention was paid to the state of preservation and only well-fixed material was considered in detail.

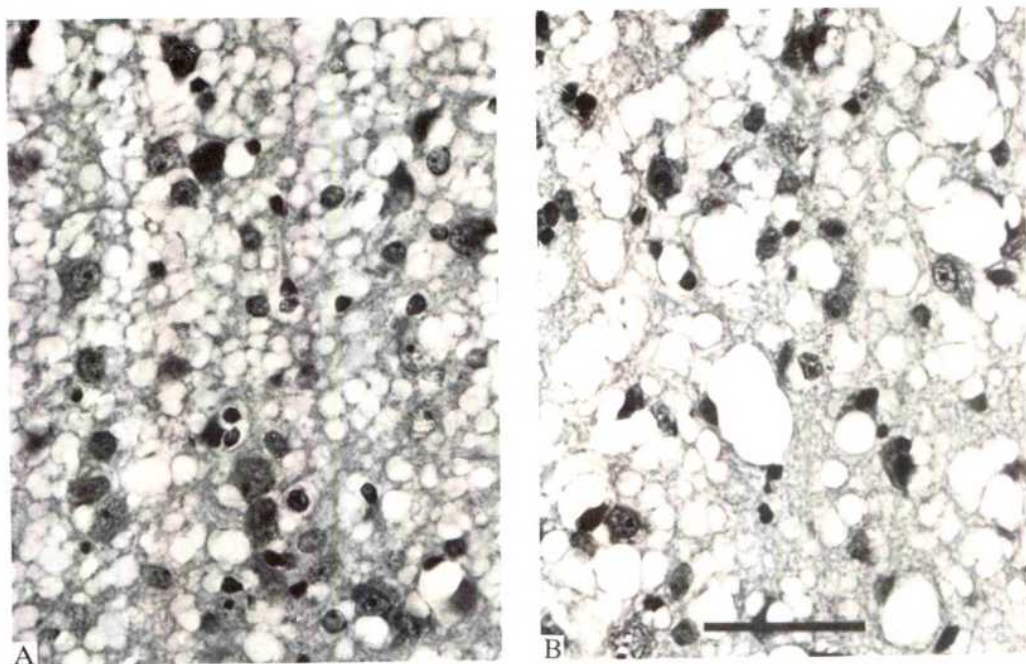


FIG. 2. The thalamus of marmosets receiving primary inoculation of brain homogenates from CJD (*Case 1*) and GSS (*Case 2*) patients. Marked spongiform change is present in these thalami. A, animal 3; B, animal 8. Haematoxylin-eosin. Bar = 50 μ m.

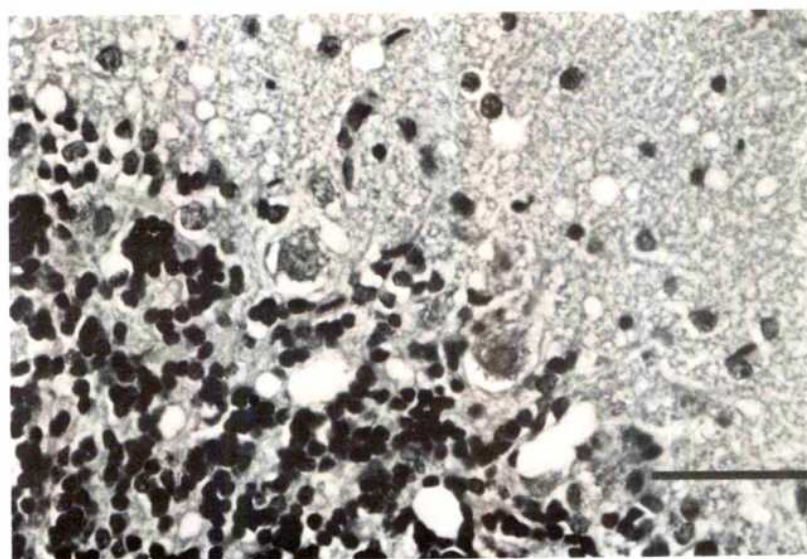


FIG. 3. Cerebellum of marmoset 8. There are scattered discrete vacuoles in molecular and granule cell layers and smaller vacuoles in perikarya of Purkinje cells. Haematoxylin-eosin. Bar = 50 μ m.

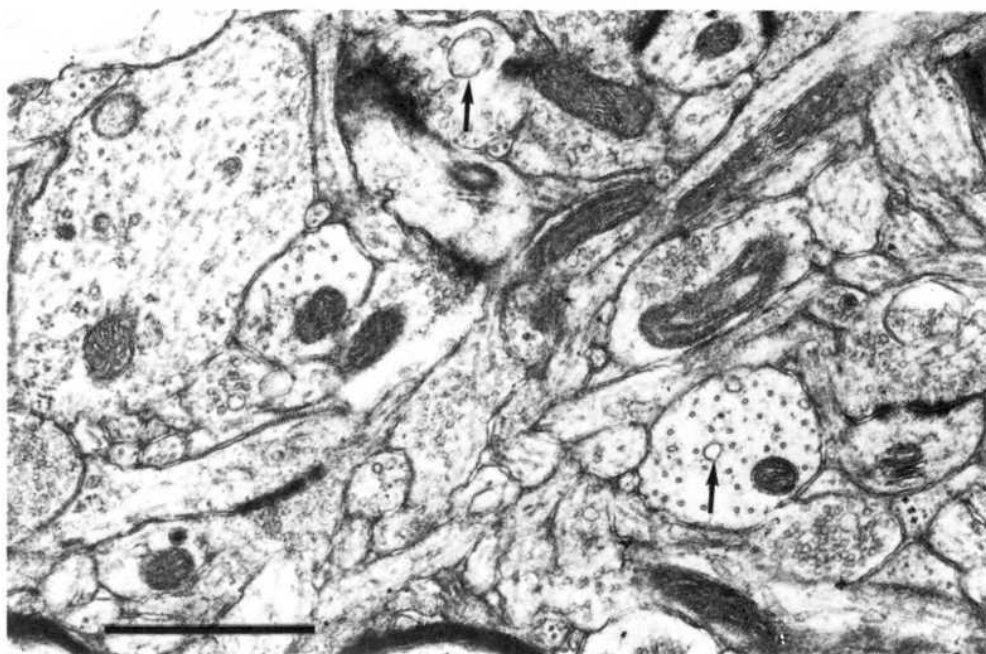


FIG. 4. Thalamus of marmoset 12 (normal control). Only occasional neuritic profiles, mostly dendrites, contain cisternae (arrows) which are evenly rounded or oval. Bar = 1 μ m.

Experiment VII (marmosets 14–19; time course of development of SE)

These experimental inoculations were made in order to study the development of pathology in the thalamus, knowing from previous study of animals 1–10 that the thalamus is invariably the region showing the most severe degree of spongiform change in the fully-developed disease. Animals 14, 15 and 16 were clinically behaviourally normal when anaesthetized and perfused with glutaraldehyde 3–8 months after inoculation, but marmoset 17 showed some abnormal behavioural characteristics for 1 wk before being killed. This abnormal behaviour consisted of eating directly off the floor of the cage, i.e., not holding food in the hands. In all other respects this animal's behaviour was normal. Animal 18 was noted to be unusually quiet and not moving much around the cage for some days while animal 19 had shown severely abnormal behaviour after an initial period of 13 months incubation during which its behaviour was normal. This marmoset therefore showed evidence of neurological disease for 9 months, eventually becoming severely affected, before it was killed 22 months postinoculation.

Sampling of the tissue and the recognition of artefact due to imperfect fixation posed considerable problems. Animal 14 was not used for electron microscopy because perfusion with glutaraldehyde under anaesthesia was obviously unsuccessful. In the other cases in which perfusion seemed to be satisfactory it was apparent from examination of the 1 μ m sections stained with toluidine blue that in some regions blood vessels contained red cells while close by capillaries and small arteries and veins were completely cleared of red cells. Many blocks were taken of the thalamus in each animal and both light

microscopy of resin-embedded tissue as well as electron microscopy were confined to the areas showing good fixation. Myelin fixation, however, remained a problem and fixation artefact affecting the myelin sheaths was seen in every case.

Marmoset 19 (22 months incubation)

The spongiform encephalopathy was very marked (fig. 5). By light microscopy it could be seen that vacuoles lying in the neuropil ranged from 2 to 20 μm in diameter, larger coalescent spaces being irregular in shape and up to 40 μm in the largest diameter. Some tiny vacuoles lay within myelinated axons, and many of the neurons contained vacuoles in their perikarya. Many neurons were distorted or surrounded by large vacuoles and some of these may have been within the neuronal cytoplasm. Some neuronal nuclei were shrunk and the nuclear membrane irregularly indented. A careful search was made for intranuclear vacuolation as described by Kim and Manuelidis (1983, 1986). None, however, was seen. Almost all except the very tiny vacuoles were rounded, presumably spherical, in shape and contained many smaller rounded vacuoles within them.

With the electron microscope the vacuoles could be seen to be bounded by a continuous membrane and within the large vacuoles were smaller ones, also membrane-bound and varying considerably in shape. Their membranes were single and thin and did not resemble mitochondrial membranes. Amorphous granular material was present in some vacuoles, others appearing quite clear. The shape of the smaller secondary spaces was most irregular and did not suggest that they were vesicles containing stored material which would more likely be spherical because of distension within them. Their limiting membrane could, in places, be seen to be in continuity with the membrane surrounding the whole space. Breaks in these limiting membranes, however, were common. The granular material did not seem to be distributed in any regular pattern.

The size of the vacuolar spaces, as visualized with the electron microscope, varied considerably. Those which were 10 μm or less in diameter tended to be rounded and discrete but the larger ones became, in many cases, confluent with adjacent vacuoles giving irregular dumb-bell-like shapes to some of the larger spaces. The larger these spaces were the more smaller membrane-bound structures lay within them. Another characteristic of the larger vacuoles, those 10 μm or more in diameter, was that they contained no identifiable remnants of organelles such as tubules, mitochondria or synaptic vesicles and their membranes had no synaptic thickenings which might have rendered their structural location or origin identifiable. However, some vacuoles of about 2 μm diameter did have remnants of postsynaptic thickenings of the peripheral membrane suggesting that they were dendrites while others contained some synaptic vesicles characteristic of axonal terminals.

As suggested by light microscopy, some neurons contained membrane-bound irregularly shaped spaces varying in size. In addition cytoplasmic clearings, not membrane-bound, were also present. These contained granular amorphous material and were mostly situated in the periphery of the neuronal perikaryon.

Between the vacuoles normal-looking axons, axonal terminals and dendrites were present in abundance. Some of these identifiable neuritic profiles, however, contained cisternae of varying size and shape, from rounded vacuoles or vesicles of about 100 nm diameter as seen in sections of controls to larger irregularly shaped membrane-bound spaces resembling those seen within the major vacuoles.

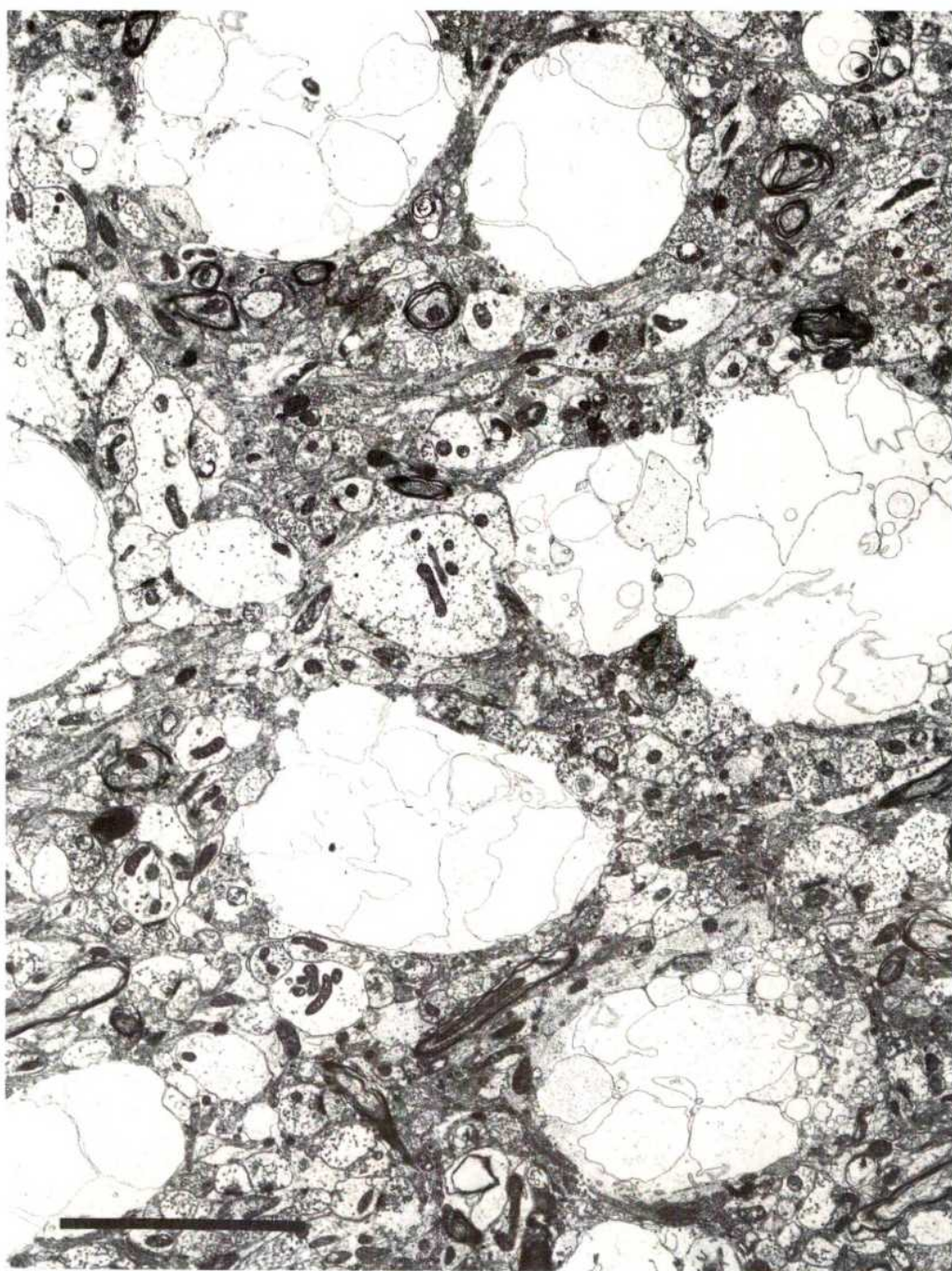


FIG. 5. Thalamus of marmoset 19 (22 months incubation). Large complex vacuoles contain many smaller membrane-bound irregularly-shaped spaces within them. The structures occupied or replaced by the vacuoles cannot be clearly identified. Bar = 5 μ m

Numerous astrocytes were identified and there were abundant profiles containing bundles of glial filaments. Evidence of degeneration of neuronal elements was present in the form of neuritic profiles containing dense bodies and multivesicular bodies; densely stained pyknotic material probably lying within macrophage processes; neurons lacking organized Nissl bodies; neuronal nuclei located peripherally in the cell and showing deep indentations of the nuclear membrane; and myelinated axons showing changes characteristic of wallerian degeneration. No inflammatory reaction was found. Capillary vessel walls had a normal endothelial cell lining, their basal lamina was of normal thickness and their external surface covered by astrocytic processes containing bundles of fibrils. Occasional large vacuolar spaces seemed to abut on capillary walls but whether these were of glial origin could not be determined.

Regions of the brain of marmoset 19 outside the thalamus were studied by light microscopy only, the brain having been secondarily fixed in formalin and embedded in paraffin wax after the initial perfusion-fixation with glutaraldehyde. The appearances were very similar to those described for animals 1–10, with spongiform changes widely dispersed throughout the brain and with very marked differences in severity from one area to another. The vacuoles in cortex (everywhere including molecular layer of cerebellum) were small and discrete, but in the basal ganglia they were larger and some were becoming confluent while in the thalamus the tissue was largely replaced by a spongy, lacy mesh of vacuoles. A careful search was made for intraneuronal perikaryal and nuclear vacuoles in the paraffin sections with particular emphasis on the Purkinje cells, but none was found.

Marmoset 18 (18 months incubation)

This animal had shown behavioural changes of a mild degree, having been unusually quiet and not moving around the cage much but otherwise showing little sign of illness.

Light microscopy of the thalamus as well as electron microscopy showed changes of spongiform encephalopathy which were very similar to those described for marmoset 19. The description of the electron microscopic appearances given above could equally well be applied to animal 18. It was hoped that the degree of involvement judged by size and numbers of vacuoles might be less because of the shorter incubation time, but it was not possible to differentiate the thalamus of the 2 animals qualitatively. Examination of the paraffin sections showed severe involvement of the putamen and small vacuoles scattered in the deeper layers of cerebral cortex and also in the molecular layer of the cerebellum.

Marmosets 15–17

Examination of the toluidine blue stained 1 μ m sections as well as of the paraffin sections did not show vacuoles which could be recognized with confidence as abnormal. The perfusion with fixative causes distension and emptying of capillaries and small rounded spaces visible may well have been capillaries.

Electron microscopy of several regions of the thalamus of all 3 marmosets showed widespread changes of a nature which might well have been considered as nonsignificant or artefactual had it not been for the obvious pathological importance of the vacuolation in the thalami of marmosets 18 and 19. Very many neural processes, both dendritic as well as axonal, particularly axonal terminals, contained vacuoles (figs 6, 7). These

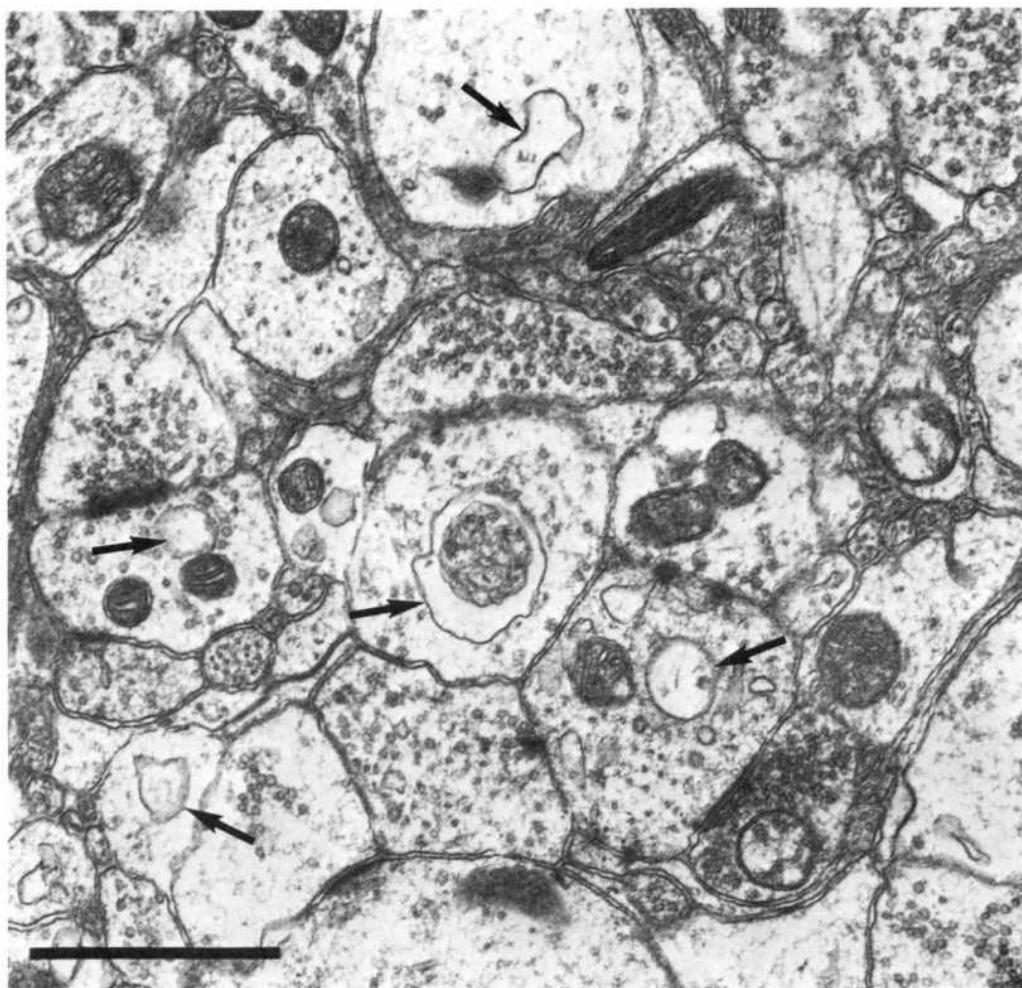


FIG. 6. Thalamus of marmoset 17 (13 months incubation). Many of the neural profiles contain membrane-bound cisternae (arrows) which are mostly irregularly shaped. Some profiles containing cisternae can be identified as axonal or dendritic and organelles and synapses are well-preserved with the exception of occasional cleared mitochondria. There is no excess extracellular space. Bar = 1 μ m.

were membrane-bound and ranged in size from a diameter of about 100 nm to 1 μ m or more. The smaller ones were evenly rounded and were exactly like cisternae of smooth endoplasmic reticulum commonly found in normal controls. The larger spaces were irregular in outline and some contained smaller vacuoles or cisternae within them. In some neural processes (usually dendrites) cut longitudinally, multiple small vacuoles were observed. Most of the neuronal profiles which contained these vacuoles could be identified and contained normal-looking mitochondria, tubules, synaptic vesicles and pre- and postsynaptic membrane densities which allowed the differentiation between dendrites and axonal terminals. Some profiles of about 1 μ m diameter were almost completely occupied by a vacuole and could not be characterized.

Vacuoles were present in the perikarya of neurons. In some instances their appearance was highly suggestive of slightly distended and enlarged cisternae of smooth endoplasmic reticulum, being somewhat elongated serpiginous structures about 1–1.5 μm in length and of variable width. In other instances they were rounded and 2–3 μm in diameter and some contained secondary vesicular structures within them. In other respects no neuronal abnormalities were observed. Nuclei were central and normally rounded and in the perikaryon abundant well organized rough endoplasmic reticulum was present.

Capillary vessels were of normal appearance and astrocytic processes containing fibrils were not especially numerous, or noteworthy. No evidence of neuronal or myelin degeneration was observed.

A careful search was made for the multilamellar plasma membrane abnormalities described by Beck *et al.* (1982), particularly in relation to the cisternae or vacuoles in dendrites. These were not seen.

It seems that the large vacuoles characteristic of the fully developed spongiform encephalopathy are derived from the cisternae of smooth endoplasmic reticulum. They are present in small numbers in the normal, are increased in size and found in increasing numbers of neuronal processes with longer survival time until they become large and confluent and are associated with degeneration of neurons and their processes in the late stages of disease. It was of interest that the change observed between 8 months and 18 months was very much greater than between inoculation time and 8 months survival, suggesting an acceleration of the enlargement of the vacuoles after 8 months of incubation.

DISCUSSION

Transmission of spongiform encephalopathies by inoculation of cerebral and noncerebral tissues is a well-known phenomenon. The diseases known to be transmissible include scrapie, mink encephalopathy, bovine spongiform encephalopathy, kuru and Creutzfeldt-Jakob disease (CJD). These diseases all share some features, either in the naturally occurring state or in the host animal in experimental transmission, and the neuropathological similarities and differences have been reviewed by Beck and Daniel (1987). The syndrome of Gerstmann-Sträussler-Scheinker (GSS) is characterized by inherited cerebral amyloidosis, with or without amyloid angiopathy, associated with spongiform encephalopathy. The neuropathological features of GSS have been described by Gerstmann *et al.* (1936), Boellaard and Schlote (1980) and Adam *et al.* (1982), the latter describing several members of the Wo. family of whom Case 2 was one. Transmission from cases of GSS has been reported by Masters *et al.* (1981) and Tateishi *et al.* (1984). One of the transmissions reported by Masters *et al.* (1981) used brain tissue derived from a member of the Wo. family who had died after 1 yr of illness characterized by progressive dementia and myoclonus, typical of sporadic CJD. The case described by Tateishi *et al.* (1984) was more typical of GSS in that there was a 4–5 yr history of progressive neurological disease comparable with our Case 2 and with very similar pathology. Transmission was to mice.

Attempts at transmission from the brain of another member of the Wo. family have not resulted in encephalopathy (Masters *et al.*, 1981), although some doubt exists about the correct identification of the material inoculated. We have also attempted transmission

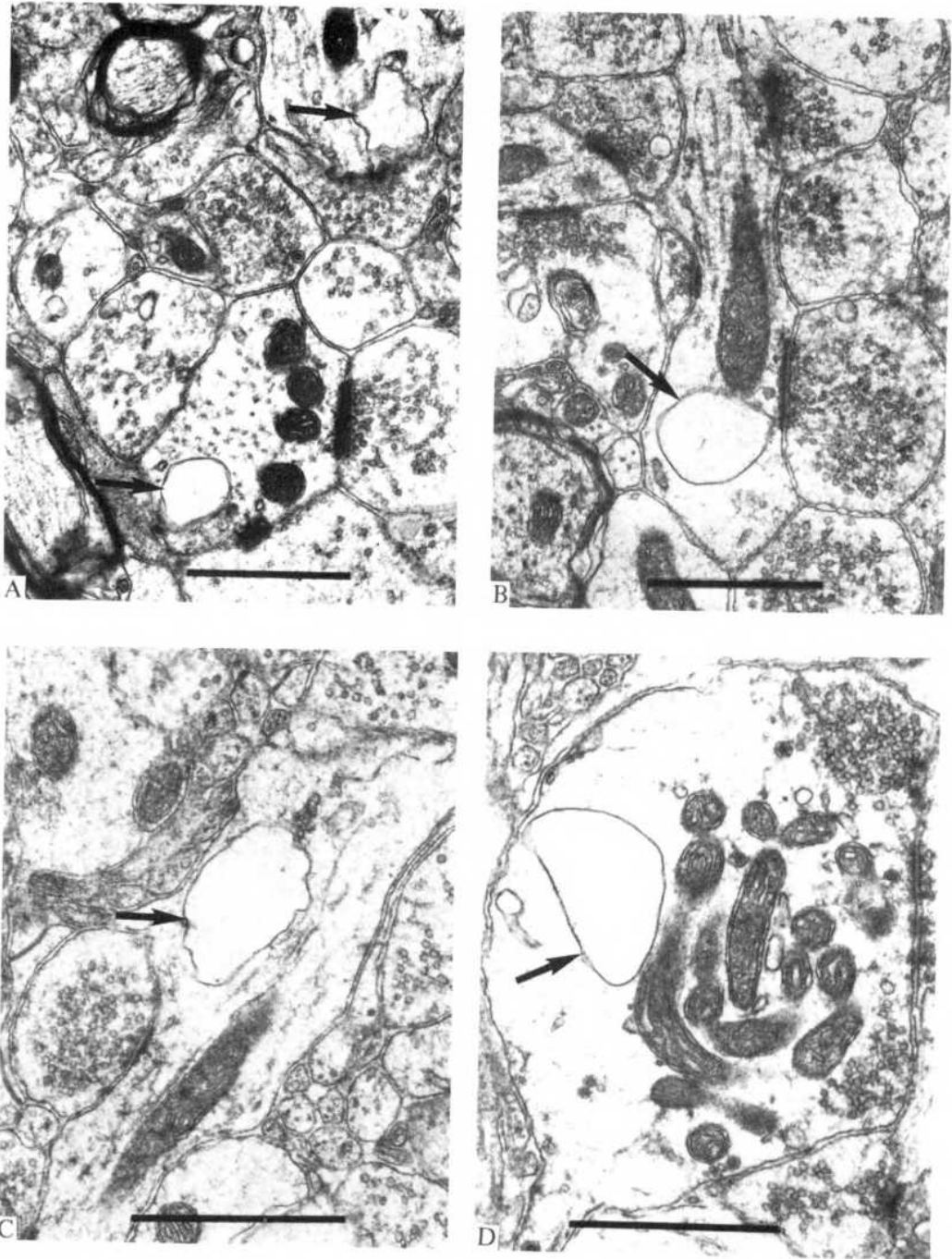


FIG. 7. Thalamus of marmoset 16 (8 months incubation) (A-D) and of marmoset 15 (3 months incubation) (E-G). Membrane-bound cisternae (arrows), some very irregular in shape, are present in many of the neural profiles. Mitochondria are generally well fixed as are microtubules, vesicles, synapses and membranes. Bars = 1 μ m.

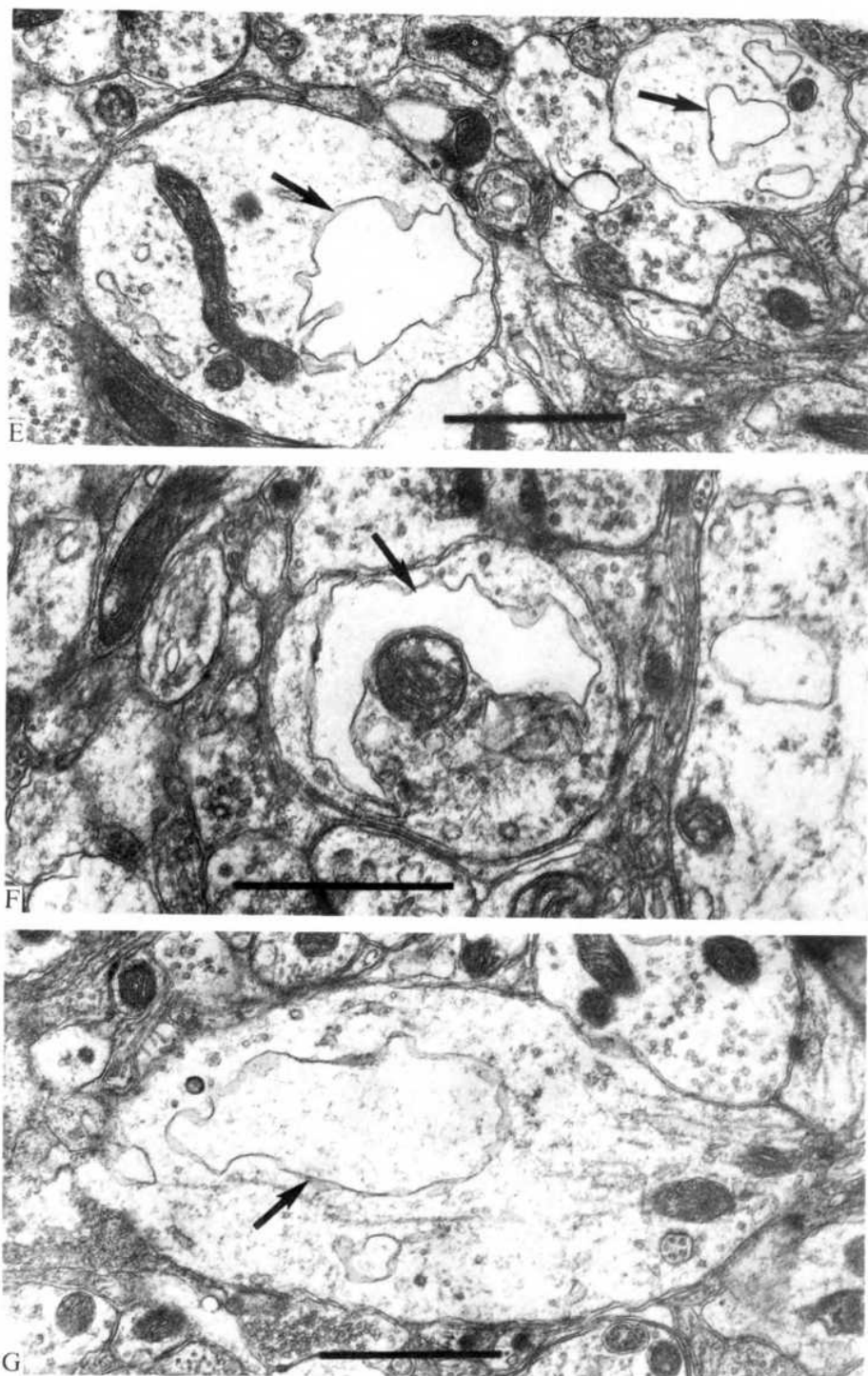


FIG. 7.E-G

from this case to marmosets but 5 yrs after inoculation there is still no evidence of encephalopathy.

One of the aims of the present work was to compare transmission from a case of CJD with that from GSS as well as to study the pathology in animals receiving passaged material by intracerebral inoculation. The human case of CJD had a short illness (8 wks) and the brain showed typical spongiform changes. Amyloid was not a feature. The animals receiving primary inoculations all showed the greatest severity of spongiform pathology in the thalamus with varying degrees of cortical involvement. Mostly the occipital cortex was only slightly vacuolated. In contrast to these the brain of the marmoset receiving passaged inoculum showed severe occipital cortical involvement including the calcarine cortex, in addition to the severe thalamic pathology. The findings in the GSS-inoculated group were almost exactly similar with the passaged inoculum inducing severe occipital sponginess, again including the calcarine cortex. Although there were few animals involved and only one passaged inoculation in each group, it does seem as if passaging changed the pattern of cerebral pathology in the recipient animal. The incubation time in the 2 passaged animals, 17 months, was identical and in both was shorter than the incubation time after primary inoculations. Although the GSS case was characterized by a very long illness (6 yrs or more), the experimentally-induced disease was of the same order as that caused by the CJD-derived inoculum. No amyloid was identified in any of the animals even though amyloid deposition in cerebral and cerebellar grey matter was a striking feature of the pathology of the original human GSS case.

Few serial studies of experimental transmission of spongiform encephalopathy have been reported in the literature. Fraser and Dickinson (1968) described the sequential development of the pathology of scrapie transmitted to mice. They used light microscopy only and followed the increasing severity of neuronal vacuolation and spongiform change. Beck *et al.* (1975) examined with electron microscopy the early changes of experimentally transmitted kuru in the brain of the spider monkey, incubation periods ranging from 4 to 40 wks postinoculation. Many nonspecific changes were described and binucleated neurons were interpreted as early evidence of pathology developing within 4 wks. A large dendrite with intracytoplasmic vacuoles was illustrated at 8 wks after inoculation comparable to those described here. Sato *et al.* (1980), in serial studies of mice inoculated with human CJD, observed severe white matter changes, including vacuolation of myelin sheaths, and later identified vacuoles in neurites. They saw no differences in the ultrastructural quality of vacuolation in early stages from those in the later stages except that with time the number of vacuoles increased. They suggested the origin of the vacuoles was from mitochondria, an interpretation which has not been considered likely in the present experimental material. Bruce (1981), using light microscopy, followed the development of amyloid plaques and vacuolation in the mouse brain following the intracerebral inoculation of scrapie agent, noting that the extent of both forms of pathology depends on both the strain of the scrapie agent as well as of the mouse genotype. Amyloid plaques appeared as early as 60 days postinoculation. Both plaques and vacuolation increased slowly in severity up to 200 days and then showed a sharp and progressive increase in number with advancing stages of the illness. Beck *et al.* (1982) reported their ultrastructural findings in the brains of spider monkeys inoculated with human kuru-brain homogenates and surviving 2–122 weeks postinoculation, all but 1 animal remaining clinically normal and free of neurological signs. Abnormal lamellated

plasma membranes of neuronal, mainly dendritic, processes were described particularly in the early stages of incubation. It was thought that these membranous abnormalities gave rise to intraneuronal vacuolation, thus preceding the development of spongiform changes and constituting an important pathogenetic step in the evolution of the disease.

These membranous changes were subsequently considered to be artefactual, the result of staining with saturated aqueous uranyl acetate, by Gray (1985). Whether this interpretation is correct or not, a particular search was made in the marmoset brains under study in the present work for multilamellated configurations but these were not observed. It must, however, be borne in mind that the inoculated material as well as the experimental animals were quite different from those studied by Beck *et al.* (1982) and the shortest survival was 13 wks as opposed to 2 wks in their experiments. A serial ultrastructural study by Kim and Manuelidis (1986) of guinea pigs inoculated with passaged material from CJD also did not reveal the presence of multilamellated membranes. That study reported occasional vacuoles visible by light microscopy at 8 wks increasing until there were many at 24 wks; electron microscopy showed swollen postsynaptic dendrites with partial clearing of the matrix and some dendrites containing small membrane-bound vacuoles, very similar to those described in the present paper, at 8 wks. Gaps in plasma membranes and swollen clear processes were also described, as were focal clearings of perikaryal cytoplasm in neurons and intranuclear vacuolation. The significance of the latter is not certain. No mention was made by Kim and Manuelidis (1986) of changes in axonal terminals, as we have seen, although in an earlier description of the fully developed experimental disease in guinea pigs Kim and Manuelidis (1983) observed vacuoles in axons as well as dendrites and neuronal and myelin degeneration which we have also observed in the longest-surviving marmoset.

The problems of the interpretation of electron microscopic appearances of the CNS raised by imperfect or delayed fixation are now well known to microscopists. Many of the earlier ultrastructural studies of spongiform encephalopathy were dogged by the interpretation of artefact as significant pathological change. Even apparently successful perfusion may not necessarily result in generalized successful fixation. Criteria for assessing adequate fixation must include at least the good preservation of membranes and intraneuronal organelles such as mitochondria, microtubules and endoplasmic reticulum, the absence of excessively distended extracellular space and the absence of distended clear astrocytic processes. In the most advanced stages of spongiform encephalopathy many of the structures of the grey matter are disrupted and distorted by the large vacuoles and there is abundant degeneration of neuronal elements as well as astrocytic hyperplasia and an abundance of glial fibril formation in astrocytic processes. All who have studied fully developed spongiform encephalopathy, whether in naturally occurring or experimentally transmitted disease states, have observed very similar changes. Landis *et al.* (1981) paid special attention to the interpretation of intracytoplasmic and dendritic or axonal vacuoles as being of significance only when they are multiple and in a region that is relatively well preserved. These criteria were followed carefully in the present experiments and the early appearance of excessive numbers of vacuoles in neuronal processes is considered to be significant and of essential importance in the pathogenesis of spongiform encephalopathy. The cautious conclusion reached by Gray (1986), that the vacuolation is the product of fixation of previously abnormal dendrites in which disassembly of microtubules had already occurred, seems unlikely

to be the case in the marmoset brains fixed by perfusion. One reason for this being unlikely is that the vacuoles are so very large and confluent but remain membrane-bound. Furthermore, evidence that spongiform change occurs as an antemortem event is presented by brains of human cases of CJD in which the cortex may be collapsed and atrophic, without evidence of necrosis, as was noted in the case from which the disease was first transmitted to chimpanzees (Beck *et al.*, 1969).

The presence, normally, of cisternae of smooth endoplasmic reticulum in the neuronal perikaryon as well as in dendrites, axons and axonal terminals, is well known. They appear in published illustrations of these structures in the normal CNS (Peters *et al.*, 1976) and are seen in our own control material. In the normal, the cisternae are not numerous and are small, rounded or oval and rather regular in shape. In the experimental animals at 3–13 months reported here, vacuoles were present in very many neuronal processes, so that in any one field the majority of dendrites and axonal terminals contained one or more. Their shape was irregular and on occasion almost filled the neurite. At 18 and 22 months the vacuolation was so marked as to be visible easily on light microscopy. We interpret the gradual increase in number and size of vacuoles as the essential element in the development of spongiform encephalopathy. What causes these changes and what the vacuoles contain within them is at present not known but the function of such cisternae and their metabolic role in the normal CNS must be important considerations in understanding the mechanisms of the development of spongiform encephalopathy.

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BOOK REVIEWS

The Effective Clinical Neurologist. By Louis R. Caplan. 1990. Pp. 370. Cambridge, MA: Blackwell. Price £23.95.

This is an unusual textbook. The author, a distinguished North American clinician and teacher of great experience, is deeply concerned about the decline in the practice of traditional clinical skills. He provides persuasive evidence that such methods—detailed history, careful meticulous physical examination followed by analysis of the particular patient's predicament—are no longer sufficiently emphasized in the training of medical students and young doctors. He attributes the deterioration to many causes but particularly to the consequences of current training and educational systems which stress the supremacy of the neurosciences rather than the humanities; rapid and profound technological advances, complex investigations and sophisticated diagnostic gadgetry conspire to distract the student from his patient. The author epitomizes the predicament by drawing attention to the fact that erstwhile departments of clinical neurology have now become those of the neurosciences. He also argues that clinical skills cannot flourish in a climate influenced by economically orientated considerations. More succinctly, he states that diagnostic procedures pay more than time spent in exercising clinical skills. There is decreasing incentive, he claims, for spending time with patients. He is not alone in drawing these disturbing conclusions; recently an American colleague pithily and sadly commented that 'histories are out, they ain't cost effective'.

Fortunately, the author does not accept the inevitability of these changes and has written a book to explain, justify and advocate the crucial importance of clinical methods in neurology. Richly embellished with illuminating case histories, aphorisms, anecdotes and lessons learnt from his teachers and from his patients, he pleads his case in an intriguing and engaging manner. I suspect this book will persuasively convince the most sceptical of tyros that he can only ignore clinical skills at his peril. If he is not sufficiently convinced, there is a fine chapter on medicolegal problems that can so easily emerge when these skills are neglected.

While the problem and its resolution are seen primarily from a North American viewpoint, recent political and economic changes in the organization of medicine and clinical neurology on this side of the Atlantic suggest that we cannot afford to be smug. The book is written in a relaxed and entertaining manner, can be profitably absorbed during a quiet evening and will be recommended by those who lament with comparable concern and passion that the traditional methods of neurology are losing the battle with the allure of the neurosciences.

GERALD STERN

Neurology: What shall I do? By Dafydd Thomas and Bev Daily. 1989. Pp. 115. Guildford: Butterworths. Price £6.95.

This small paperback is the second in a series produced by Butterworths under the title 'What shall I do?' Already the question of ophthalmology has been addressed and in this book, Dr Thomas from St Mary's Hospital with Dr Daily, his general practitioner colleague, consider many of the problems current in neurological practice. The idea of a question and answer book of this type is somewhat unique. I feel it does fulfil a role for there are many questions here that are posed not only by the general practitioner but by the patients. A browse through this book will give a good indication of the current feeling with regard to many simple clinical problems.

Questions regarding the disadvantages of epilepsy are put concerning diagnosis and restrictions on lifestyle. The question of driving and epilepsy is considered. Headache is given a significant number of questions and head injury, together with the authors' views on the posttraumatic syndrome. Following these early subjects other important neurological topics such as dementia, spinal cord problems and infections are considered and under weakness, fatigue and narcolepsy we have the author's views on the lively topic of myalgic encephalomyelitis—he favours the significance of the virus protein I (VP1) test. In all, the general practitioner poses 100 questions. The questions are succinct and direct and the answers sufficiently short and precise to justify a recommendation for most neurologists to read through this volume to judge

his own general clinical practice against that of the authors. I do not feel there is much here with which orthodox practice would disagree.

Under 'Useful addresses' the various charitable and neurological societies are listed and an index gives access to the various topics considered.

All in all a useful little book, cheap at £6.95, certainly in the lightweight division of the neurological literature, but interesting and helpful nevertheless.

J. B. FOSTER

The Genetics of Neurological Disorders. Second edition. By Michael Baraitser. 1990. Pp. 733. Oxford: Oxford University Press. Price £30.00.

The disciplines of clinical neurology and genetics have a substantial area of common interest. Dr Baraitser's first edition of this book provided an authoritative reference for practitioners of both specialities. Since the first edition in 1982 there have been huge advances in molecular genetics that have made an increasing contribution to clinical practice, demanding a second edition to take account of these changes.

Rather than devoting a separate section to 'new genetics' the author describes the new techniques in their application to Huntington's disease and Duchenne muscular dystrophy. The underlying theory and laboratory methods receive less emphasis. A problem which is inherent to a book of this type is that the march of science ensures that the text is outdated by the time it reaches the bookshelves. Abnormalities of the dystrophin gene, for example, can now be investigated by new methods, including immuno-histochemistry, PCR and by more comprehensive restriction enzyme analysis. The book mentions the recent mapping or sequencing of the genes responsible for myotonic dystrophy, Friedreich's ataxia, familial amyloid polyneuropathy and inherited spongiform encephalopathy, but the clinical implications are left to the reader to investigate.

The strength of this book lies in the scholarly treatment of both old and new literature pertaining to familial neurological diseases. The author's style is clear and good use is made of tables. Where relevant, case reports and epidemiological evidence are discussed critically. This is supported by the exhaustive list of references which occupies the last 200 pages of the book. Because of the thorough treatment of the literature the structure of the book is much closer to a reference book than a textbook; it is difficult to read an entire chapter. Each chapter is devoted to a logical group of disorders which aids the reader in search of a differential diagnosis. I found the chapter on the degenerative diseases of childhood particularly valuable, showing that new genetic and biochemical data can clarify a difficult clinical classification.

The author's aim clearly is to furnish the reader with sufficient information to give accurate and full counselling to patients at risk of the neurological diseases described in the book. He succeeds. The section on Huntington's disease contains useful guidelines on the counselling process which is so important to the practice of the clinical geneticist.

The book can be heartily recommended as a work of reference to the clinician seeking information on the genetics of neurological disease.

SIMON HAMMANS

Immunological Mechanisms in Neurologic and Psychiatric Disease. Edited by Byron H. Waksman. 1990. Pp. 336. *Research Publications: Association for Research in Nervous and Mental Disease*, Volume 68. New York: Raven Press. Price \$144.00.

This volume ably fulfils the aim of the Association for Research in Nervous and Mental Disease to keep clinicians informed of developments in immunological aspects of neurology. The deliberations of experts at the 1988 annual symposium are recorded in more than 20 chapters, most of which can stand alone as succinct and authoritative reviews of active fields of current research. For the uninitiated the book begins with helpful accounts of virology and immunology. Lapkin and others summarize how viral infections may affect the nervous system, sometimes down-regulating metabolism of specific groups of neurons without inducing an inflammatory response. Hafler offers an excellent crash course on immunology in 14 pages including 2 figures. Then follow chapters on diseases or groups of diseases sharing immunological abnormalities.

Engel and colleagues show with elegant immuno-electron micrographs how nonnecrotic muscle fibres are invaded by the CD8+ lymphocyte subset in polymyositis: they argue that cytotoxic T cells are the prime movers while in dermatomyositis antibody-mediated damage to muscle capillaries is more important. Raine honestly admits that the evidence that multiple sclerosis is an autoimmune disease is limited to its histological resemblance to experimental allergic encephalomyelitis and that a worldwide 40 year long search has not revealed specific autoantibodies or cell-mediated immune reactions to myelin antigens. On the other hand, specific autoantibodies recently identified in some rare disorders are likely to be pathogenetically relevant and are already diagnostically important. In the stiff man syndrome, briefly mentioned in a chapter by Richman and others, there are antibodies to glutamic acid decarboxylase which is rate limiting in GABA synthesis. An authoritative chapter by Posner and Furneaux reviews the antibodies to Purkinje cell cytoplasmic antibodies in paraneoplastic cerebellar degeneration, antibodies to neuronal nuclei in paraneoplastic subacute sensory neuropathy, antibodies to a different neuronal nuclear antigen in paraneoplastic opsoclonus myoclonus, and antibodies to retinal ganglion cells in paraneoplastic retinal degeneration. Antibodies to myelin-associated glycoprotein and myelin glycolipids in the demyelinating neuropathy associated with 'benign' IgM paraproteinaemia are reported by Latov. Antibodies to the acetylcholine receptor protein in myasthenia gravis and to the presynaptic voltage-gated calcium channels in Lambert-Eaton syndrome are described by Newsom-Davis. The book was written before the flood of reports of antibodies to gangliosides in lower motor neuron disorders had washed over the printing presses. Some patients with lower motor neuron disorders do have antibodies to ganglioside GM₁. Although some patients with such antibodies have been reported to respond to experimental treatment with sufficient intravenous cyclophosphamide to cause total alopecia, the patients who have responded have had multifocal conduction block and may have had chronic idiopathic (inflammatory) demyelinating polyradiculoneuropathy. We have now shown that such antibodies may be present in high titre in patients with Guillain-Barré syndrome and are strongly associated with poor outcome (Doherty, Cronin, Walsh, Koblar, Hughes and Winer, unpublished information). Unfortunately, patients with paraneoplastic central nervous system degeneration and autoantibodies to relevant neurons have not so far responded to immunosuppressive treatment or removal of an associated neoplasm. Since central neurons do not regenerate effectively we may need to identify these syndromes and institute treatment earlier before irreversible damage has been done.

Every general medical and neurological library will need this book. Biological psychiatrists will be tantalized because immunological research in their field remains not so much infantile as embryonic. One hopes that the immunology of psychiatry will not turn out to be the phantasmogoric oxymoron which Brown uses in the last chapter (written before 'mad cow disease' had made neurology headline news in the United Kingdom) to describe the immunology of transmissible spongiform encephalopathy.

RICHARD HUGHES

Pain Syndromes in Neurology. Edited by H. L. Fields. 1990. Pp. 286. London: Butterworths. Price £39.50.

This book presents a problem: for whom is it written? The editor has aimed to throw light on three areas: the normal anatomy and physiology of pain, the pathophysiology of damaged sensory neurons, and finally the diagnosis and treatment of patients with neuropathic pain. I think he has succeeded in his intention, in that the individual contributions deal well with these topics, but the book has surprisingly been entitled *Pain Syndromes in Neurology*, which is misleading and unfortunate.

The chapters are excellently written, up-to-date and well referenced. It is good to see a chapter on postherpetic neuralgia, a topic often avoided in neurological textbooks, although the promise of topical capsaicin referred to in this chapter has subsequently receded. There are useful summaries on reflex sympathetic dystrophy and peripheral neuropathies (although the latter omits HIV infection as a currently important cause of painful peripheral neuropathy), perhaps illustrating how few advances have been made in the clinical management of chronic pain conditions. Surgical management is discussed at length, and it must be evident from the sheer number of destructive and modulating procedures described how restricted is their role and unpredictable their benefits and side-effects, particularly for nonmalignant pain. A review of dorsal root entry zone (DREZ) lesion procedures for deafferentation pain syndromes resulting from brachial plexus avulsion, paraplegia and postherpetic neuralgia indicates rather unpredictable benefit in comparatively small numbers of patients; the chapter includes some particularly good illustrations.

Whether advances will come through serendipity or through basic research is unclear, but for an

understanding of underlying mechanisms, Devor and Rappaport's chapter on 'Pain and the pathophysiology of damaged nerve' is excellent (although virtually only processes in peripheral nerve are considered), and Field's introductory chapter provides an outstanding overview of the state of the art. Other chapters summarize mechanisms of hyperalgesia and sensitization of primary afferent fibres; the role of the sympathetic nervous system and in particular the contribution of the wide-dynamic-range neurons sensitized by nociceptive input; the diagnosis of cancer pain; and the present use of drug therapy in chronic pain, including a consideration of the controversial use of opiates in chronic nonmalignant pain.

The book is timely, reasonably priced, and a valuable addition to available books on the subject. It is probably of greater benefit to those already interested and wanting an up-to-date review of various topics related to mechanisms and management, rather than to those who wish to familiarize themselves with pain syndromes in neurology.

G. D. SCHOTT

Motor Disturbances II. Edited by A. Berardelli, R. Benecke, M. Manfredi and C. D. Marsden. 1990. Pp. 440. London: Academic Press. Price £50.00.

This book is made up of a series of selected papers presented at the Second Congress of the International Medical Society of Motor Disorders, held in Rome in June 1988. While the title is an all-embracing 'Motor Disturbances II', this book deals predominantly with physiological studies on extrapyramidal disorders and motor neuron disease. In particular, there is emphasis on magnetic and electrical stimulation of the brain, and many of the papers in this book employ electromyographic techniques to address new and old problems of disordered physiology in disturbances of motor function. In addition, clinical observations are correlated with physiological changes, and there are several papers on positron emission tomography. Neuropathology and neuropharmacology receive minimal coverage, but this deficiency is likely to be corrected in future congresses, which will incorporate more North American contributors.

The majority of papers are summaries of current work by experts, and as such they constitute a useful, compact reference source for neurologists involved in the study of disease of the motor pathways. This volume is of particular value to those who have an interest in movement disorders and motor neuron disease, but who were unable to attend the ISMD Congress. It is not a comprehensive monograph on motor disturbances, and it is perhaps unfortunate that the title does not reflect the rather specialized nature of the book.

DONALD CALNE

Diabetic Neuropathy. Edited by J. Ward and Y. Goto. 1990. Pp. 604. Chichester: John Wiley. Price £65.00.

This book is based on a collection of 71 papers given by 282 international contributors at a meeting on Diabetic Neuropathy held in 1988 in Singapore. The papers cover some clinical, morphological, biochemical, physiological and therapeutic aspects of diabetic neuropathy. Rather than providing a complete overview of the area, the book informs the reader of recent investigations by different teams around the world.

In the Introduction, Professor P. K. Thomas reviews critically the different pathogenetic concepts for diabetic neuropathy and reaches the conclusion that, in spite of a large body of evidence in favour of a vascular basis, both for focal and for generalized diabetic polyneuropathy, for the latter 'a number of arguments are in favour of an alternative mechanism or cast some doubt on the conclusion that vascular factors are the major component in the chain of causation that results in nerve fibre loss'. He then reviews the pathogenetic hypotheses and concludes that the 'myo-inositol deficiency hypothesis, which provided an enormous stimulus, can now be discarded'. Therefore, other hypotheses remain and further research is needed.

Section I deals with clinical aspects and Section II is devoted to morphological studies on human and experimental diabetic neuropathies. The paper by Sharma and colleagues on morphological abnormalities in the sural nerves of patients with symptomatic neuropathy or with subclinical peripheral nerve involvement is interesting and well illustrated. Then there is a series of papers on nerve lesions in experimental diabetes. It is interesting to note that Julu found no dimensional differences in the node of Ranvier in the cutaneous

nerves of normal and streptozotocin-diabetic rats. The author observed 'axoglial dysjunction', which represents the structural basis of experimental diabetic neuropathy for Sima *et al.*, in only 3/250 nodes of Ranvier. Among the experimental models, the WBN/Kob rat seems promising, with obvious morphological abnormalities in the sciatic nerve shown by Mori *et al.*

Section III contains papers on biochemical aspects of diabetic neuropathy, with several communications on therapeutic trials with different aldose reductase inhibitors including Alrestatin, Ponalrestat and ONO-2235. Hotta *et al.* report on a favourable effect of ONO-2235 on some neuropathic symptoms in a 24 month long, but unfortunately uncontrolled, study. In another paper, Suzuki *et al.* found that aldose reductase inhibitors normalized functional and morphological abnormalities in Goto-Kakizaki rats, but the numerous artefacts of the myelin sheaths, due to poor fixation, present on the photograph of the sciatic nerve of an untreated diabetic control rat, cast some doubt on the reliability of the morphological observations.

In Section IV, the paper by P. A. Low on vascular and hypoxic factors in chronic experimental and human diabetic neuropathy provides a good summary of the large amount of work performed by the author in the field. In a paper on the pathogenesis of human diabetic neuropathy, Malik *et al.* observed no alteration of nerve sorbitol/fructose in diabetic patients, but found that nerve microvascular abnormalities were significantly associated with neuropathic severity.

Section V is made up of a collection of papers on the evaluation of diabetic neuropathy. I enjoyed reading the contribution by Abraham and Levy on 'Measurement and quantitation' in which the authors evaluate critically the methods currently in use and indicate ways in which they might be refined. The problem of the specificity and sensitivity of the different methods of evaluation of diabetic neuropathies is well discussed.

Section VI is devoted to autonomic neuropathy and Section VII deals with potential treatments of diabetic neuropathy. Five papers claim some beneficial effect of methylcobalamin on human and experimental diabetic neuropathy. Then there is a series of 6 papers reporting beneficial effects of treatment with gangliosides on different aspects of diabetic neuropathy, including axoplasmic transport, autonomic disturbances and symptoms of diabetic neuropathy. Readers not familiar with morphology of peripheral nerves must be informed of the inversion of the legends for figs 2 and 3 in the paper by Paro *et al.* Favourable effects of PGE₁, of ginkgolavonglycosides and of folic acid on some manifestations of diabetic neuropathy are also reported.

Section VIII deals with various pathophysiological considerations and therapeutic approaches to the diabetic foot, including an open trial, with favourable results, on the local use of fish oil.

We hope that these treatments will prove beneficial for patients with diabetic neuropathy, even though the rationale for the use of some of them is not obvious. Most readers will find a few chapters of great interest, some of peripheral interest but most only of minimal interest, in this expensive book.

G. SAID

Hepatic Encephalopathy: Pathophysiology and Treatment. Edited by Roger Butterworth and Gilles Pomier Layrargues. 1989 Pp. 621. Clifton, NJ: Humana Press. Price £83.85.

This volume, which is published as part of the experimental biology and medicine series, draws together the current theories of the pathophysiology and treatment of hepatic encephalopathy. The 40 chapters summarize the work presented at a symposium held in Val David, Quebec, in late 1988 and are reproductions of the authors' original papers. The text is frequently repetitive and suffers from a lack of cohesion. The variety in type face, chapter layout and reference formatting is not appealing and is all the more surprising in view of the length of time it has taken for the volume to appear. Such poor production could be excused only if it were 'state of the art' information being published within weeks of the symposium ending. Nevertheless, the editors have assembled an impressive group of experts in the field of hepatic encephalopathy and the chapters are on the whole authoritative pieces. They have allowed a reasonable balance in the space allocated to the various theories of the pathophysiology of encephalopathy.

The book contains much information of current interest and is a useful source of references up to 1988. It essentially summarizes the research of many of the key contributors to the field of hepatic encephalopathy and will be helpful to those embarking on research work of their own. However, a word of caution for

the uninitiated in this area. Although a few chapters try to take a balanced overview, the majority express the individual preferences of the authors concerned.

ROGER WILLIAMS

Clinical Neurology for Psychiatrists. Third edition. By David M. Kaufman. 1990. Pp. 526. Philadelphia: W. B. Saunders. Price £50.00.

This book begins with a very brief reminder on how to perform a neurological examination, followed by chapters on central nervous system disorders, psychogenic neurological deficits, cranial nerve impairments, peripheral nerve disorders, muscle disorders, dementia, aphasia and related disorders, headaches, seizures, cerebrovascular disorders, visual disturbances, congenital cerebral injuries, neurological aspects of pain, and sexual function, multiple sclerosis, sleep disorders, movement disorders, brain tumours and metastatic cancer, ending with investigations such as lumbar puncture and neuroimaging techniques. The text is concise, easily readable and is supplemented by tables, figures and drawings. After each chapter a list of references and both short-answer and multiple-choice questions (MCQs) and their answers are given. At the end of the book there are an additional 322 questions and answers. Those who like MCQs and this way of learning will find this aspect of the book particularly useful. Although there are some omissions, this is a quick, well organized and easy reference book. The main drawback is the price (£50.00). This is excessive, especially when one considers other books covering broadly the same topics, such as the indispensable Lishman (1987, *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder*, Second edition, Oxford: Blackwell) and standard neurology textbooks.

MARY M. ROBERTSON

Some Pitfalls and Problems in Neurosurgery. Edited by J. C. de Villiers. 1990. Pp. 208. Basel: Karger. Price £82.50.

This book is the 13th edition in the series *Progress in Neurological Surgery*. It is unusual in that rather than describing technical neurosurgical information on new techniques, etc., it concentrates on describing the pitfalls that may occur at every level from the diagnosis through to the operation and subsequent postoperative phase. That complications may occur during any surgical procedure will be admitted even by the most experienced neurosurgeons. The editor has collected some very experienced neurosurgeons who describe the problems and pitfalls that they have encountered over the years within their own particular subspecialty of neurosurgery.

The book itself consists of 6 chapters which describe complications associated with transphenoidal surgery, problems with cerebrospinal shunting, the surgery of intramedullary spinal lesions, pitfalls in the management of lumbar disc disease and an invaluable chapter on the pitfalls and problems in the diagnosis of cerebral death. There is also a chapter by the hugely experienced neurosurgeon Emil Pasztor from Budapest, describing the surgical complications following frontal and temporal approaches to basal tumours. Although this chapter is excellent I felt it was over long for a book of this size.

This book has been written with the neurosurgical trainee in mind in order that the years of experience accumulated by the contributors, particularly in relation to neurosurgical problems, can be disseminated in a step by step analysis of surgical events. It will also be an invaluable text for young neurosurgeons beginning their consultant career.

ROBERT BRADFORD

Management of Posttraumatic Spinal Instability. Edited by Paul Cooper. 1990. Pp. 319. Park Ridge, IL: American Association of Neurological Surgeons. Price \$80.00.

This is the first book in a series based on the idea that the American Association of Neurological Surgeons should provide neurosurgeons with periodic publications related to neurosurgery.

The first 3 chapters are concerned with the early assessment, clinical assessment and imaging of patients with spinal injury. The first chapter contains some excellent algorithms for the management of cervical

spine and thoracolumbar spine injury with and without neurological deficit. Orthopaedic and neurosurgeons in the UK who may see spinal cord injury infrequently would find these invaluable. The chapter on imaging in spinal injury is also well written and up-to-date. The book then concentrates on the management of spinal injury at each level of the vertebral column from occipitocervical instability down to a slightly unusual chapter on the management of sacral fractures. Two chapters are then devoted to special problems in patients with pre-existing spinal disease and spinal stabilization in children.

The content and emphasis of the book clearly reflects the more interventional North American practice in spinal cord injury and I feel that it is a method of management which is rapidly gaining acceptance in the UK, certainly amongst neurosurgeons and orthopaedic surgeons with a particular interest in spinal surgery. Although a good proportion of the book deals with the internal fixation techniques used in stabilizing the injured spine, interestingly the majority of the contributors are again neurosurgeons, reflecting North American practice.

The book will be of interest both to orthopaedic and neurosurgeons who have on occasion to deal with the consequences of spinal injury, but will also be of value to those who consider themselves spinal surgeons, whether orthopaedically or neurosurgically trained.

ROBERT BRADFORD

Neuro-oncology. Edited by David G. T. Thomas. 1990. Pp 303. Sevenoaks, Kent: Edward Arnold. Price £50.00.

This book is similar in concept to the book on brain tumours edited by David Thomas and David Graham and published in 1980. There have been considerable changes in the authorship and the present volume consists of 15 chapters written by authors mainly from London, but also from the United States and Sweden.

Although the first sentence of the preface states that the outlook for patients with primary malignant brain tumours remains gloomy, a degree of guarded optimism pervades most of the contributions. The book begins with a chapter on the *in vitro* biology of human brain tumours in which Darling has written a comprehensive account of tissue culture of gliomas with lists of cell lines and a compendium of methods. There is a section on *in vitro* testing of chemotherapeutic agents, a difficult area when dealing with tumours that show wide heterogeneity in their phenotypic and genotypic characteristics. Continuing with the theme of basic biology of brain tumours, Westermarck *et al.* have contributed an excellent chapter on oncogene expression and control of growth in malignant brain tumours. There is a basic account of the functional aspects of oncogenes and their interplay with antioncogenes in neoplastic development. This is followed by a more detailed review of oncogenes in gliomas and the suggestion that growth factors and their receptors are potential targets for therapeutic intervention.

Watkins and other members of Mark Noble's group in London contribute a very useful summary of their work on glial cell markers in CNS development and human gliomas. In this chapter, the authors expand on the hypothesis that the major factor controlling growth of gliomas within the brain might be an interplay between tumour cells and normal cells in the immediate microenvironment. The last chapter in the basic biological section is by Lantos and Pilkington and deals with pathology of experimental brain tumours. Much of the chapter is concerned with the induction of tumours by nitrosourea compounds and a summary of the contribution that this technique has made to the understanding of neuro-oncology. Oncogenic viruses, radiation and transplantable tumours are also covered in this chapter.

The next 5 chapters are mainly concerned with the clinical presentation, investigation and diagnosis of human brain tumours. There is a succinct contribution on the pathology of brain tumours by Barnard in which he discusses some of the merits of the various classifications that are available. A particularly useful chapter in a time of rapidly advancing imaging technology is the assessment of neurological imaging of brain tumours by Kinsley, who points out that it is often difficult to decide whether CT or MRI is the method of choice. In his accounts of these techniques he discusses such a choice in some detail. As a pathologist, it is heartening to read that the ultimate diagnosis of a brain tumour still rests with obtaining histological material.

The *in vivo* metabolism of human cerebral tumours is covered in a chapter devoted to positron emission tomography (PET) by Brooks. His account of this technique for studying oxygen and glucose metabolism and the haemodynamics of human cerebral tumours ends on the optimistic note that PET provides a means for studying the kinetics of uptake of labelled cytotoxic agents by tumours and so optimizing their

administration. PET may also be suitable in the future for studying cerebral tumour receptors and it may thus play a part in the development of more specific anticancer agents. This section ends with succinct chapters on the epidemiology of brain tumours by McKeran *et al.* who volunteered that no useful preventative advice can be offered to reduce the incidence of brain tumours. Finally, there is a summary of the clinical manifestations of brain tumours.

The last, and largest section, comprising half the book, is devoted to surgical and medical therapeutic aspects of brain tumours. Bradford and Thomas deal with the advances in surgery for malignant brain tumour, ranging from techniques for CT and MRI-directed stereotactic biopsies to the sophisticated methodology employed for computer-interactive stereotactic tumour excision. They emphasize the increasing importance of stereotactic microsurgery in the management of malignant gliomas. A wide-ranging chapter on brain and spinal cord tumours in children has been contributed by Tobias and Haywood. In their succinct and well-referenced contribution these authors cover not only tumours in all parts of the brain and spinal cord but also pituitary tumours and the effects of these tumours on the rest of the brain. They also review many of the diagnostic and therapeutic aspects. In a chapter on radiotherapy and the treatment of cerebral astrocytomas, Leibel and Sheline deal with early and late reactions of the brain to radiation and give an account of therapeutic trials in the treatment of astrocytoma, anaplastic astrocytoma and glioblastoma multiforme. They include an interesting section on the classification of astrocytic gliomas in which they suggest that the Kernohan grading system is of little use, whereas the histological classification of tumours into pilocytic astrocytoma, astrocytoma, anaplastic astrocytoma and glioblastoma has considerable prognostic importance. There are two detailed chapters on chemotherapy and biological response modifier therapies in malignant gliomas by Dropcho, Mahaley and Gillespie in which the authors review the response of brain tumours to various chemotherapeutic and immunological regimes. With the rapid development of agents and techniques in these fields, the authors look forward to the evolution of successful, efficacious antiglioma therapy in the future. Finally, there is a chapter by Wheildan and McKeran on the terminal care of brain tumour patients in which they point out that given the limited success and the treatment of malignant brain tumours, the patients' best interests might be served by consideration of approaches and facilities for the care of the terminally ill patient. This chapter deals with management of the many distressing symptoms that develop in glioma patients and the suffering induced in patient and relatives by the inevitable fatal outcome of many brain tumours.

This book is a very interesting and, for its size, a wide-ranging treatise on primary malignant brain tumours. There is little overlap between the various chapters and the authors have been carefully chosen. If there is any criticism of the book, it is a mild degree of inconsistency, particularly in the classification of tumours. Some authors use one system whereas others use a different one. This probably reflects the heterogeneity of brain tumour classification and nomenclature which, in some degree, bedevils the whole subject.

I would thoroughly recommend this book to scientists, physicians and surgeons who have an interest in the study, treatment and management of brain tumours.

R. O. WELLER

New Trends in Ageing Research. Edited by G. Pepeu, B. Tomlinson and C. M. Wischik. 1988. Pp. 237. Berlin: Springer. Price DM 98.00.

Although one would not expect it from the title, this book originates from a meeting on brain ageing held in April 1987. Unavoidably, many of the contributions are out of date and more recent advances are not covered in the book. For example, important progress has been made in knowledge of amyloid formation and breakdown, as well as in the genetics of Alzheimer's disease. Also not included is reference to current work on the role of the glycine binding site of the NMDA receptor which has modified views about the action of excitatory amino acids in the brain. This is relevant as glutamergic neurons are implicated in the pathology of Alzheimer's disease.

The editors have identified fundamental questions in the interdisciplinary field covered in the book. What are the fundamental physiological changes in ageing of the central nervous system? What is the rational therapeutic approach to the ageing brain? A major problem in attempting to answer these questions is the relationship between normal and pathological ageing for there is no suitable animal model of Alzheimer's disease. It appears that in ageing rodents there is reduced plasticity in many neuropeptide and monoamine synapses; in some brain areas evoked release of catecholamine is impaired. However, it is not known

if this happens in the ageing human brain. Changes in behaviour and neurochemistry in relation to age-related neurodegeneration are the subject of several chapters but this also may not be relevant to normal ageing of the human brain and only to restricted aspects of the pathogenesis of dementing disease. One possible closer model of dementia is produced by lesioning the basal forebrain in rats with subsequent loss of cholinergic neurons followed by long-term changes in the serotonergic system. Compared with rodents, there are less marked changes in the cholinergic system in the elderly human cortex; moreover in Alzheimer's disease, damage possibly originating in the olfactory system may extend to large cortical neurons secondarily affecting the subcortex rather than degeneration beginning in the basal nucleus. In old rats there is loss of choline acetyltransferase-positive neurons, and degenerative changes (e.g., perikaryal cross-sectional area) are seen in surviving nerve cells. It is claimed that these changes can be prevented by feeding phosphatidylserine, although the mechanism of this effect is uncertain. In addition to contributions on these topics other articles related to neuroendocrinology and immunity emphasize the multidisciplinary nature of research on brain ageing.

ALAN N. DAVISON

Alzheimer's Disease. *Advances in Neurology*, Volume 51. Edited by R. J. Wurtman, S. Corkin, J. H. Growdon and E. Ritter-Walker. 1989. Pp. 310. New York: Raven Press. Price \$106.50.

Alzheimer's disease is receiving wide coverage both in the medical and lay press and it is not surprising that the *Advances in Neurology* series, which had not produced a title dealing with dementia since 1983, has made it the subject of its latest volume. The interest Alzheimer's disease generates is due to its high prevalence and to the hope that advances in the neurosciences will lead to a better understanding of its pathophysiology and to effective treatment. Unfortunately this promise remains largely unfulfilled. Scientific advances in the last few years have given us a better understanding of its epidemiology and has enabled us to distinguish it more accurately from other dementias, but the findings of linkage studies remain controversial, the application of molecular biology to the study of plaques and neurofibrillary tangles is inconclusive and the outcome is still as hopeless as ever.

By concentrating on the abnormalities of cholinergic transmission, the largest part of the book stays on relatively firm ground and these chapters provide a good introduction to the review of various treatment approaches and possible future therapeutic strategies. Other sections deal with clinical, epidemiological and pathological studies, genetics and molecular biology and, more succinctly, with cognitive abnormalities. The chapters are very brief (I counted 41 in less than 300 pages of text) and the contributors, predominantly American, number over 150. This makes for a book that reads like the proceedings of a symposium, although there is no indication that this was its origin. The chapters, which often follow the standard format of papers submitted to journals, are uniformly informative even if at times they overlap or appear to be unrelated to the surrounding contributions. An introductory chapter in each section linking the individual contributions would have been welcomed, but as it stands the book provides an up-to-date review of many promising areas of research, some of which may produce important contributions in the future.

MARIA RON

Neurobiology of Panic Disorder. Edited by J. C. Ballenger. 1990. Pp. 391. New York: Wiley-Liss. Price \$96.00.

This volume, published as part of the *Frontiers in Neuroscience* series, is devoted entirely to biological aspects of Panic Disorder (PD). A companion volume on clinical aspects of panic disorder is to follow. A reading of the current volume leaves one with the feeling that the less ambitious approach of a single volume covering both biological and clinical aspects of PD would have been more worthwhile. The material, in 23 chapters, covers well-trodden approaches in biological psychiatry including sections on genetics, neurotransmitter systems and neuroimaging. The volume lacks unifying coherence and the boundaries implicit in the title are frequently crossed by the presentation of material on generalized anxiety and depression. This is not altogether surprising given that the nosological status of PD as a distinct entity is not universally accepted, particularly on this side of the Atlantic. A firm separation between PD and both generalized anxiety and agoraphobia is still a matter of controversy. The presentation of a convincing clinical basis

for separating PD from related anxiety disorders would have been a help in putting some of the material in perspective. One is left to wonder how a nosological entity such as PD, not listed in ICD-9 but first given separate status in DSM-III, can now command so much attention and research. A sceptic's viewpoint is that it represents a transatlantic tendency to justify nosological inventiveness dictated in no small part by peculiarities of American medical practice.

R. J. DOLAN

Brain Repair. Edited by A. Björklund, A. J. Aguayo and D. Ottoson. Wenner-Gren International Symposium Series, Volume 56. 1990. Pp. 385. Basingstoke: Macmillan. Price £55.00.

For more than five years, there has been a yearly international meeting, in different cities, of people working with animal models for the repair of brain injury. Historically, the meetings have developed from and around two main themes—the anatomical and functional consequences of transplantation of embryonic tissue into adult rodent brain (and especially the use of dopaminergic replacement in animal models of Parkinson's disease), and the use of peripheral nerve grafts as axonal bridges. A further topic arising from these approaches is the study of NGF and other growth and trophic factors (especially in relation to central cholinergic mechanisms). More recently, interest has also started to be taken in the role of glial cells, and the description of normal development of pathways (spinal cord, visual system, and hindbrain segmentation) as well as some molecular events, such as the production of growth-associated proteins.

Brain Repair is a bound set of 26 camera-ready manuscripts from the latest such meeting in Stockholm in May 1989. The short articles provide an excellent overview—or directory—of a large and representative selection of current work in this field, and a starting point for entering the vast literature of fully refereed articles and short reviews which all the contributors to this book have published in the archival journals.

The present volume will be of potential interest to those who are newly entering the field now, or who would like a quick snapshot-type view of how things stand at the moment. It makes last year's volume out of date, and it will itself become out of date within a year. As an abstract volume or directory, it is more focused than, say, the comprehensive American Neuroscience Meeting Abstracts, or a library literature search, and portable, and the brevity of the articles makes it possible for the reader to scan through a large segment of the field at one reading.

G. RAISMAN

Molecular Neurobiology. Edited by D. M. Glover and B. D. Hames. *Frontiers in Molecular Biology*. 1989. Pp. 203. Oxford: Oxford University Press. Price £25.00 (hardback), £18.00 (paperback).

Frontiers in Molecular Biology is a series which has already produced several useful books. This one illustrates, in 3 main chapters, how molecular biology is being applied to understanding the specialized proteins of the nervous system. The preface by E. A. Barnard discloses the width of the subject and the limitations imposed on any small book that seeks to provide representative examples. For example, Table 1 lists 16 different protein types that are essential for neuronal function. These can be roughly grouped into two classes; developmental/structural (e.g., morphogens, adhesion molecules, growth factors) and transmission (axonal transport proteins, synthesizing enzymes, various ligand-gated and voltage-gated receptors, classified in Table 2, and ion channels). It is a little disappointing that the chapters in this book are not more representative of this diversity. Although they illustrate very well the different approaches that can be used, there is some overlap in terms of the molecules concerned.

B. Ganetzky and C.-F. Wu describe in detail how classical and molecular genetics, including 'strategies for cloning genes', 'isolation of mutants' and 'germ line transformation', have been used to identify genes involved in phototransduction, cholinergic transmission and muscle function in *Drosophila*. Various mutations affect opsins, choline acetylase, acetylcholine esterase, and sodium and potassium channels. As the authors conclude, these mutations 'provide an unparalleled set of tools for dissecting the process involved in neural signalling'. In addition, the components involved are homologous with their mammalian equivalents, so that genetic sequences from *Drosophila* can be used to identify the equivalent genes in mammals. A good example is that of the potassium channel which was first cloned from *Shaker* mutants, and subsequently used to identify potassium channel homologues in rat and mouse brain.

T. Claudio's chapter summarizes the structure, pharmacology, and electrophysiology of ligand-gated and voltage-gated ion channels, and describes the classical biochemical/molecular biological approach to their purification, cloning and characterization, with particular reference to the acetylcholine receptor (AChR). This chapter describes particularly well the application of different *in vitro* systems (e.g., *E. coli*, *Xenopus* oocytes, yeast and stable mammalian cell-lines) for expressing natural and mutant forms of the AChR cDNAs for functional studies. This way of correlating predetermined molecular structure with function contrasts with the genetic analysis of behavioural mutants described in *Drosophila*.

The development and maintenance of cellular relationships are obvious key factors in neuronal function. The final chapter, by J. Covault, covers the molecular structure of cell adhesion molecules and their role in neural development. This provides many further examples of the use of molecular approaches to identify and characterize functional molecules. There is a comprehensive table listing the different proteins, how they interact, and their putative functions. Particularly fascinating are the different 'multigene families', for instance some adhesion molecules are part of an 'immunoglobulin superfamily', and the different ways in which they interact, some both homophilic and heterophilic. There is still much to learn about the control of expression and exact function of these molecules but this chapter, with many illustrative figures and sketches, provides a stimulating account.

This is not a book for the faint-hearted. Although Barnard's preface gives a fairly gentle introduction to the field, each of the main chapters is comprehensive and extensively referenced. The book is clearly intended for basic research workers, but at a relatively modest price it is well worth buying, and anyone involved in the application of molecular biology to clinical research should appreciate the way in which the book emphasizes the use of different techniques and approaches to unravel the molecular components of a complex system.

ANGELA VINCENT

Neurotoxins and Their Pharmacological Implications (A Biological Council Symposium). Edited by Peter Jenner. 1987. Pp. 315. New York: Raven Press. Price \$54.00.

This book consists of the proceedings of a Biological Council Symposium on Neurotoxins held in April 1986. Hence, it is inevitably 4 years out of date. However, it provides some useful and interesting data on the state of the art at that time. The topics covered consist of studies of excitotoxins, substances affecting ion channels, MPTP and unrelated, isolated contributions concerning botulinum toxin, capsaicin and dioxin.

Although the title suggests that the primary motivation for the conference was the mechanism of action of neurotoxins, the approach is rather the reverse—it is mainly orientated to discussions of using neurotoxins as tools to understand physiological and pathological processes. This is indeed a valid use of neurotoxins. It is interesting to be reminded how important naturally occurring neurotoxins have been in defining ion channels and unravelling their behaviour. Many of the toxins produced by snakes, insects and marine life are considered in this section.

As with any volume of symposium proceedings, subjects are not comprehensively covered. This volume is essentially for dipping into and perhaps finding at random a new piece of information about a topic of interest. The sections where several papers are devoted to a particular topic (ion channels, excitotoxins and MPTP) are likely to be more useful than the miscellaneous unrelated collection of papers in the last section, covering one small aspect of the substance.

PAMELA M. LE QUESNE

The NMDA Receptor. Edited by J. C. Watkins and G. L. Collingridge. 1989. Pp. 242. Oxford: Oxford University Press. Price £25.00

Following the immense explosion of interest in the excitatory amino acids, many symposia, books and reviews have kept us up to date with developments. The receptor identified by the selective ligand N-methyl-D-aspartate (NMDA) has perhaps excited the most intense interest. This book is the result of a symposium which formed part of the April meeting of the British Pharmacological Society last year and was dedicated to the NMDA receptor. Each chapter is contributed by one of the speakers and summarizes the recent

work from each of these laboratories. J. C. Eccles provides a forward and historical introduction to the central excitatory synapse.

The first two chapters, by J. C. Watkins and H. J. Olverman and J. C. Watkins, provide a historical introduction to the pharmacology of the NMDA receptor and describe many compounds, some now in widespread use, others more recently introduced, that are active at the NMDA receptor. Possible models for the structure of the receptor based on structure activity relations are discussed. The comprehensive summary of active compounds and their structures will undoubtedly be useful to many in the field. Noncompetitive antagonists at the NMDA receptor/channel complex, i.e., those that block responses to NMDA but do not compete for binding at the NMDA receptor itself, are discussed by D. Lodge, M. Jones and E. Fletcher. This chapter concentrates on the now familiar pharmacology of compounds that block the ion channel, but also introduces more recently categorized actions at other sites, e.g., those activated by glycine and polyamines. That even such a well-defined receptor type as that which has come to be known as the NMDA receptor may exist in more than one form is discussed by D. T. Monaghan and C. W. Cotman. Autoradiographic studies indicate that different brain regions may contain different proportions of agonist and antagonist-preferring binding sites. R. H. Evans discusses the strengths and perhaps more importantly, the weaknesses of a variety of in vitro recording techniques widely used in studies of the pharmacology of excitatory amino acids. This chapter should certainly be heeded by any about to begin such studies.

Discussion of more functional aspects of NMDA receptor/channels begins with the chapter by P. Ascher and J. W. Johnson. They discuss the evidence for Na^+ , K^+ and Ca^{++} permeability of the ion channel, its blockade by Mg^{++} at a site deep within the channel and the kinetics of agonist and antagonist binding to both NMDA and glycine receptors. J. Davies summarizes the pathways that can be shown to utilize NMDA receptors and those that cannot and stresses the importance of performing adequate pharmacological controls whenever 'selective' antagonists are used. Discussion of the functional significance of NMDA receptors is continued by N. Dale, with particular relevance to their involvement in the organization of spinal motor patterns. Interplays between NMDA receptor-mediated and voltage and/or ion gated currents are also discussed in this context. A description by G. L. Collingridge and S. N. Davies of the now well established role of NMDA receptors in the induction of long-term potentiation (LTP) in the hippocampus serves also to introduce to the behavioural studies described by R. G. M. Morris, S. Davies and S. P. Butcher. Evidence that LTP is a useful model for the cellular and synaptic changes underlying learning and memory is provided by demonstrations that NMDA antagonists disrupt the acquisition, but have less effect on retrieval and storage, of certain types of spatial memory. The general theme of synaptic plasticity is extended with a discussion of the involvement of NMDA receptors in developmental plasticity, particularly in visual cortex, by A. Artola and W. Singer. This chapter gives a comprehensive review of the importance of synaptic plasticity in the development of the visual field response properties of cortical neurons and places the contribution made by NMDA receptors in context with that made, for example, by cholinergic and adrenergic inputs. The developmental theme is continued by J. Garthwaite who discusses the involvement of excitatory amino acid receptors in promoting neuronal differentiation and neurite outgrowth in the cerebellum, even before functional synapses form. Following the formation of functional synapses there is a graded decline in the relative contribution of NMDA versus non-NMDA receptors to granule cell responsiveness. This informative description of cerebellar synaptic physiology and pharmacology ends with a discussion of excitotoxicity.

The possible involvement of NMDA receptors in pathological states and the potential usefulness of drugs designed to modify NMDA receptor function in diseases, particularly epilepsy and postischaemic brain damage, is the subject of the last 6 chapters. Epilepsy is discussed by W. A. Wilkie *et al.* and B. S. Meldrum *et al.* A wide variety of additional clinical conditions are covered by P. L. Herrling, who also discusses the important issue of potential side-effects of drugs that act on this receptor/channel. Hypoxic/ischaemic neuronal damage is also discussed by B. S. Meldrum *et al.* and by L. L. Iversen *et al.* who describe studies with some more recently developed compounds.

For those who are not yet familiar with the many facets of NMDA receptor research, this book will provide a useful introduction. The vast experimental effort presently devoted to this receptor/channel ensures that the field develops and expands at an alarming rate and no one book can cover all aspects, nor hope to be topical by the time it reaches the book stands. Several of the studies described here have since been extended in directions that shed new and sometimes different light on the questions addressed, whilst others that are simply alluded to have burgeoned to become major new areas of research. This book was published

fairly rapidly after the symposium, apparently leaving the editors with insufficient time to avoid repetitions or typographical inconsistencies. These are, however, minor problems if each chapter is studied as a separate review

ALEX M. THOMSON

Neuromethods 8: Imaging and Correlative Physiochemical Techniques. Edited by A. A. Boulton, G. B. Baker and D. P. J. Boisvert. 1988. Pp. 442. Chichester: John Wiley. Price £66.80.

The volume contains 9 chapters, written by internationally acclaimed experts in their fields, on methods of measuring and imaging cerebral function. It is aimed at neurologists and clinical neuroscientists, and chapters cover measurements of cerebral blood flow and metabolism, pial vessel haemodynamics, the theory of magnetic resonance imaging, measurement of extracellular electrolyte levels, immunocytochemical detection of neurotransmitter systems, and measurement of sensory evoked potentials. The use of diffusible gases, autoradiography, and PET to measure cerebral blood flow, oxygen, and glucose metabolism, is reviewed in detail. The way that nutritional blood flow and red cell velocity measurements complement each other is discussed, and the use of magnetic resonance both for imaging and for performing ^1H , ^{31}P , ^{13}C spectroscopy with surface coils in vivo is presented. Each chapter contains a detailed account of the theory and rationale behind its topic, a brief review of its clinical applications and, where appropriate, a guide on which equipment to use and pitfalls to avoid in analysis of data.

The volume is interesting to read and well written, and I expect it will be most appreciated by experts in one of the nine fields it covers who wish to learn a little about the other complementary areas of cerebral function. For those wishing to learn in depth about a specific topic it will serve to point the reader towards more extensive reviews of that particular area, and it highlights the immediate clinical application of each technique. A slight disappointment for me was the absence of any information on the role of autoradiography and PET for studying neurotransmitter systems, and on the potential role of MRI for studying magnetic susceptibility changes in degenerating subcortical nuclei due to iron deposition. Detailed discussions of the Fick and Sokoloff methods of measuring cerebral blood flow and glucose metabolism are also presented twice over in separate chapters which seems a little unnecessary.

In summary, this volume will be a useful addition to the neurophysiology section of any neurology library, and for workers in the field of cerebral function will provide a valuable source of references in interrelated methodology. I heartily recommend it.

DAVID BROOKS

SHORT NOTICES

The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders due to Alcoholism and Malnutrition. Second edition. By Maurice Victor, Raymond D. Adams and George H. Collins. 1989. Pp. 231. Philadelphia: F. A. Davis. No price given.

The first edition of this neurological classic was published in 1971 and was based on a series of studies on the neurological complications of alcoholism undertaken by the authors over a 20 year period at the Boston City, Massachusetts General and Cleveland Metropolitan General Hospitals. This second edition is partly based on the further clinical experience of the authors and also on the large literature that has accrued since the first edition. Topics given particular additional coverage include the effects of thiamine deficiency on the nervous system, the psychology and anatomy of the amnesic syndrome and the controversial questions of alcoholic dementia and cerebral atrophy.

Textbook of Pain. Second edition. Edited by Patrick D. Wall and Ronald Melzack. 1989. Pp. 1064. Edinburgh: Churchill Livingstone. No price given.

The first edition of this book, which was published in 1984, quickly established itself as the standard reference work both on the pathophysiology and the clinical aspects of pain. Written by everyone working in the field who matters (well, almost), its three sections cover basic aspects, clinical aspects of diseases in which pain predominates, and therapeutic aspects. Its coverage is comprehensive and critical. It is essential reading for anyone with a serious interest in the causation and management of pain.

Neurological Complications of Renal Disease. By Charles F. Bolton and G. Bryan Young. 1990. Pp. 256. London: Butterworths. £50.00.

Charles Bolton has made important contributions on the treatment of uraemic neuropathy by renal transplantation and on the syndrome of critical illness polyneuropathy. In this monograph he is joined by Bryan Young, neurologist, medical historian and clinical neurophysiologist, to produce a comprehensive, readable, authoritative and practical account of the neurological complications of renal failure and their treatment. It will be valuable not only for neurologists working in a general hospital setting, but also for nephrologists and internists.

ANNOUNCEMENTS

Ninth International Congress of Electromyography and Clinical Neurophysiology

This will be held in Jerusalem, Israel, on June 2–6, 1991. Further information may be obtained from Dr A. N. Gilai, PO Box 29334, Tel Aviv 61292, Israel.

Fifteenth International Symposium on Cerebral Blood Flow and Metabolism

This will be held at the University of Miami (James L. Knight International Center, Miami, Florida, USA) on June 1–6, 1991. Further information may be obtained from Jenny Bernal, School of Continuing Studies Office of Conferences and Institutes, University of Miami, PO Box 248005, Coral Gables, Florida 33124-1610, USA.

Fifth Annual Magnetic Resonance Imaging Conference

Organized by the Barrow Neurological Institute of St Joseph's Hospital and Medical Centre, this conference will be held on March 16–20, 1991. Further information may be obtained from Kevin King, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA.

Barrow Neurological Institute Eighteenth Annual Symposium

This symposium, which will be held at Marriott's Camelback Inn Resort, Scottsdale, Arizona, on March 21–23, 1991, will be devoted to 'Recent Advances in Neurology and Neurosurgery'. For further information, contact Tony A. Jardine, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA.

International Quincke Symposium

This symposium, organized under the auspices of the World Federation of Neurology, will be devoted to Barrier Concepts and Cerebrospinal Fluid Analysis. It will be held in Göttingen, on September 19–21, 1991. For information, contact Professor K. Felgenhauer, Neurologische Universitätsklinik, Robert-Koch-Strasse 40, D-3400 Göttingen, FRG.

British Aphasiology Society

A conference will be held at Sheffield University on September 19–21, 1991. Abstracts of papers not exceeding 150 words with an accompanying summary of not more than 500 words (2 copies of each) should be sent, by March 31, 1991, to Dr Graham Venables, Department of Neurology, The Royal Hallamshire Hospital, Sheffield S10 2TN.

American Association of Electrodiagnostic Medicine

The AAEM will be sponsoring four 'hands-on' regional workshops in the Spring of 1991 at Denver (February 22–24), Chicago (March 9–10 and 15–16) and Washington, DC (March 23–24). For details and registration form, contact the AAEM, 21 Second Street SW, Suite 306, Rochester, MN 55902, USA.

Medical College of Wisconsin

A course on 'Imaging the head, spine and musculoskeletal system: a discussion of protocols and applications' will be held at the Westin Kauai Resort in Kauai, Hawaii on February 17–22, 1991. For details, contact Marti Carter, CME Inc., 11011 West North Avenue, Milwaukee, WI 53226, USA.

Third International Workshop on the At Risk Infant

This will be entitled 'The developmental Neurobiological Basis for early intervention: animal models and human data—guidelines for practice, and will be held in Jerusalem on July 1–5, 1991. For further information, contact The Third International Workshop on the At Risk Infant, c/o International Ltd, PO Box 29313, 61292 Tel Aviv, Israel.

Euromyasthenia III

The Third European Conference on Myasthenia Gravis will be held at Wadham College, Oxford, UK on July 3–5, 1991. Further information may be obtained from Dr A. Vincent, Neurosciences Group, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK.

Focus on Epilepsy: Clinical Mechanisms and Pharmacological Approaches

An International Symposium on the basic mechanisms will be held on August 10–12, 1991, at the Hotel Le Chantecler, Ste Adele, PC, Canada. This is a satellite symposium of the IBRO World Congress of Neuroscience that is being held in Montreal on August 4–9, 1991. For information, contact Focus on Epilepsy Symposium Secretariat, 3801 University Street, Room 804, Montreal, Quebec, Canada H3A 2B4.

European Neurological Society

The third meeting will be held at the Palais de Beaulieu, Lausanne, Switzerland on June 27–July 1, 1992. The deadline for the receipt of abstracts is January 15, 1992. Further information may be obtained from Professor Andreas Steck, Service de Neurologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

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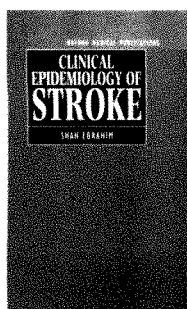
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